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(54) Title: MIMOTOPES AND ANTI-MIMOTOPES OF HUMAN PLATELET GLYCOPROTEIN Ib/IX (57) Abstract The present invention is directed to an isolated peptide that functionally mimics a binding site for a monoclonal antibody, the monoclonal antibody recognizing an epitope within the human platelet glycoprotein Ib/IX complex. This peptide is called a mimotope. The invention also provides an isolated molecule capable of binding to the peptide, or the mimotope, which molecule can be an antibody, a second peptide, a carbohydrate, a DNA molecule, an RNA molecule, or other naturally or chemically synthesized molecules. This isolated molecule is called an anti-mimotope. Mimotopes mimicking the binding site for monoclonal antibody C-34 and SZ 2, as well as anti-mimotopes to the C-34 mimotopes, are specifically provided.		

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MIMOTOPES AND ANTI-MIMOTOPES OF HUMAN PLATELET GLYCOPROTEIN Ib/IX

5 This application is a continuation-in-part of
U.S. Serial No. 06/406,330, filed March 17, 1995, the
contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

10 The present invention relates to a peptide
capable of functionally mimicking the binding site for
a monoclonal antibody (i.e. a mimotope), the monoclonal
antibody recognizing an epitope within the human
platelet glycoprotein Ib/IX complex, and to isolated
15 molecules capable of binding to the peptide (i.e. an
anti-mimotope).

BACKGROUND OF THE INVENTION

Throughout this application various
publications are referenced, many in parenthesis. Full
20 citations for these publications are provided at the
end of the Detailed Description. The disclosures of
these publications in their entireties are hereby
incorporated by reference in this application.

The platelet glycoprotein Ib/IX (GPIb/IX)
25 receptor for von Willebrand factor (vWf) is believed to
consist of a 1:1 heterodimeric complex (Du et al. 1987)
between GPIb (160 kDa) and GPIX (17 kDa) in a
noncovalent association. GPIb in turn consists of a
disulfide-linked 140 kDa alpha chain (GPIb alpha) and a
30 22 kDa beta chain (GPIb beta) (Fitzgerald and Phillips
1989).

The GPIb/IX complex comprises one of the
major transmembrane receptor complexes on blood
platelets (Roth 1991; Lopez 1994; Clemetson and
35 Clemetson 1995), mediating von Willebrand factor (vWF)
dependent platelet adhesion. The human autosomal
dominant bleeding disorder termed platelet-type von
Willebrand disease (PT-vWD) represents a naturally
occurring model of an up regulated GPIb/IX receptor

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(Miller and Castella 1982; Miller et al. 1983). In this disorder, abnormally low concentrations of the chemical modulator ristocetin are able to promote the interaction of vWF with GPIb-IX. Additionally, the platelets from such patients are aggregated at a lower shear force than required for normal platelets (Murata et al. 1993). One kindred of BT-vWD patients was found to have a single point mutation leading to a substitution of valine for glycine at residue 233 of the GPIb alpha chain (Miller et al. 1981). A second point mutation in very close proximity (substitution of valine for methionine at residue 234; Russell and Roth 1988; Takahashi et al. 1995) has been described in two additional kindreds displaying the BT-vWD phenotype (Weiss et al. 1982; Takahashi 1989).

In the 1980's, Miller et al. developed a series of monoclonal antibodies (mAb) directed against the GP Ib/IX complex receptor for vWf. In particular, monoclonal antibody C-34 was characterized in detail and it was determined that mAb C-34 recognized an epitope within the platelet glycoprotein Ib/IX complex (Miller et al. 1990). In their and subsequent work, Miller et al. showed that monoclonal antibodies C-34, AS-2 and AS-7 were potent inhibitors of the ristocetin-induced aggregation of normal platelets that was dependent upon von Willebrand factor. Miller et al. also showed that the epitopes for all three monoclonal antibodies lay within the GPIb/IX complex. Miller et al. were able to localize monoclonal antibody binding sites for AS-2 and AS-7 to the amino-terminal 45 kDa of GPIb alpha. The epitope for C-34 was recently localized to the extracellular portion of the GPIb alpha chain expressed on the surface of Chinese Hamster Ovary cells (Chambers et al. 1995). The failure of C-34 to bind to denatured GPIb alpha in Western blots (Ward and Berndt 1995; Clemetson and Hugli 1995), or to immunoprecipitate the extracellular region of GPIb alpha removed from platelets under a variety of experimental conditions (Miller et al. 1990) strongly

suggests that the epitope recognized by C-34 is highly conformation-dependent. Recently Ward and Berndt have, however, now reported the successful immunoprecipitation by C-34 of a 1•His-Arg•293 amino terminal fragment of ¹²⁵I-labeled glycoconalicin following digestion of the purified molecule by trypsin (Ward and Berndt 1995).

Attempts to define the binding sites for various monoclonal antibodies have led to the development of epitope libraries. Parmley and Smith developed a bacteriophage expression vector that could display foreign epitopes on its surface (Parmley and Smith 1988). This vector could be used to construct large collections of bacteriophage which could include virtually all possible sequences of a short (e.g. six-amino-acid) peptide. They also developed biopanning, which is a method for affinity-purifying phage displaying foreign epitopes using a specific antibody (see Parmley and Smith 1988; Cwirla et al. 1990; Scott and Smith 1990; Christian et al. 1992; Smith and Scott 1993).

After the development of epitope libraries, Smith et al. then suggested that it should be possible to use the bacteriophage expression vector and biopanning technique of Parmley and Smith to identify epitopes from all possible sequences of a given length. This led to the idea of identifying peptide ligands for antibodies by biopanning epitope libraries, which could then be used in vaccine design, epitope mapping, the identification of genes, and many other applications (Parmley and Smith 1988; Scott 1992).

Using epitope libraries and biopanning, researchers searching for epitope sequences found instead peptide sequences which mimicked the epitope, i.e., sequences which did not identify a continuous linear native sequence or necessarily occur at all within a natural protein sequence. These mimicking peptides are called mimotopes. In this manner, mimotopes of various binding sites/proteins have been

found. LaRocca et al. (1992) expressed a mimotope of the human breast epithelial mucin tandem repeat in *Escherichia coli*. Balass et al. (1993) identified a hexapeptide that mimics a conformation-dependent binding site of the acetylcholine receptor. Hobart et al. (1993) isolated a mimotope that mimics the C5 epitope (the epitope for the sixth component of complement).

The sequences of these mimotopes, by definition, do not identify a continuous linear native sequence or necessarily occur in any way in a naturally-occurring molecule, i.e., a naturally occurring protein. The sequences of the mimotopes merely form a peptide which functionally mimics a binding site on a naturally occurring protein. For example, the mimotope of Balass et al. (1993) mimics the binding site of the acetylcholine receptor.

Many of these mimotopes are short peptides. The availability of short peptides which can be readily synthesized in large amounts and which can mimic naturally-occurring sequences (i.e., binding sites) offers great potential application.

A need continues to exist, therefore, for the elucidation of useful mimotopes.

SUMMARY OF INVENTION

This need is met by the mimotopes of the subject invention. The invention thus provides an isolated peptide that functionally mimics a binding site for a monoclonal antibody, the monoclonal antibody recognizing an epitope within the human platelet glycoprotein Ib/IX complex. This isolated peptide is a mimotope. A peptide functionally mimics a binding site for a monoclonal antibody if the monoclonal antibody can bind to the peptide.

The invention further provides an isolated molecule capable of binding to the peptide, which molecule can be an antibody, a second peptide, a carbohydrate, a DNA molecule, an RNA molecule, or any

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chemically synthesized molecule, for example. This isolated molecule is an anti-mimotope. Anti-mimotopes that bind to a receptor can be used to mediate the functional activity of that receptor.

5 The invention thus also provides a method for modulating the adhesion, aggregation, or agglutination of platelets, each of which is dependent on von Willebrand factor interaction with platelets through the glycoprotein Ib/IX complex receptor. The methods
10 provide for exposure of platelets to the molecule (anti-mimotope) in order to modulate adhesion, aggregation, or agglutination of the platelets.

 The invention further provides an isolated peptide capable of binding to monoclonal antibody C-34,
15 as well as an isolated molecule capable of binding to such peptide. Also provided is a method for modulating the adhesion, aggregation, or agglutination of platelets by exposing the platelets to the molecule (anti-mimotope).

20 In a preferred embodiment, the isolated peptide capable of binding to monoclonal antibody C-34 includes an amino acid sequence corresponding to SEQ ID NO:38: WNWRYEYV.

 The invention still further provides an
25 isolated peptide capable of binding to monoclonal antibody SZ-2, as well as an isolated molecule capable of binding to such peptide. Also provided is a method for modulating the adhesion, aggregation, or agglutination of platelets by exposing the platelets to
30 the molecule (anti-mimotope).

BRIEF DESCRIPTION OF THE DRAWINGS

 These and other features and advantages of this invention will be evident from the following
35 detailed description of preferred embodiments when read in conjunction with the accompanying drawings in which:

 Fig. 1 illustrates the ristocetin-induced full aggregation of platelets in the presence of von Willebrand factor;

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Fig. 2 illustrates the inhibition of ristocetin-induced aggregation of platelets by 20 μ g/ml of monoclonal antibody C-34;

5 Fig. 3 illustrates the continued inhibition of ristocetin-induced aggregation of platelets by 20 μ g/ml of mab C-34 in the presence of 0.14 μ M of the synthetic peptide mimotope having SEQ ID NO: 1: AWWNRYREYV;

10 Fig. 4 illustrates the partial neutralization of the inhibition of ristocetin-induced aggregation of platelets by 20 μ g/ml of mab C-34 in the presence of 0.27 μ M of the synthetic peptide mimotope having SEQ ID NO: 1: AWWNRYREYV;

15 Fig. 5 illustrates the partial neutralization of the inhibition of ristocetin-induced aggregation of platelets by 20 μ g/ml of mab C-34 in the presence of 0.55 μ M of the synthetic peptide mimotope having SEQ ID NO: 1: AWWNRYREYV;

20 Fig. 6 illustrates the partial neutralization of the inhibition of ristocetin-induced aggregation of platelets by 20 μ g/ml of mab C-34 in the presence of 1.1 μ M of the synthetic peptide mimotope having SEQ ID NO: 1: AWWNRYREYV;

25 Fig. 7 illustrates the complete neutralization of the inhibition of ristocetin-induced aggregation of platelets by 20 μ g/ml of mab C-34 in the presence of 2.3 μ M of the synthetic peptide mimotope having SEQ ID NO: 1: AWWNRYREYV;

30 Fig. 8 illustrates the functional screening of candidate anti-mimotope bacteriophage clones. Following incubation of 150 μ L of the indicated bacteriophage clones with 250 μ L of citrated PRP for 1 hr at 22°C, aggregation was initiated by the addition of 0.8 mg/mL ristocetin under stirring conditions at
35 37°C;

Figs. 9-11 illustrate the effect of synthetic peptides upon ristocetin-induced aggregation of formalin-fixed platelets; and

Figs. 12a-12c are a diagrammatic sketch of mimotopes and anti-mimotopes used to probe the structural relationships in platelet glycoprotein Ib/IX complex.

5

DETAILED DESCRIPTION

The invention provides an isolated peptide that functionally mimics a binding site for a monoclonal antibody, the monoclonal antibody
10 recognizing an epitope within the human glycoprotein Ib/IX complex. This peptide is called a mimotope.

In one preferred embodiment, the monoclonal antibody is designated C-34, and the peptide includes an amino acid sequence selected from the group
15 consisting of:

	SEQ ID NO:1:	AWNWRYREYV
	SEQ ID NO:2:	KWNWRNKKYV
	SEQ ID NO:3:	LSTWRYFEYV
20	SEQ ID NO:4:	YLGWRYSEYV
	SEQ ID NO:5:	TQMWRAREYL
	SEQ ID NO:6:	WRQREYWDPV
	SEQ ID NO:7:	EGSWRYRKGG
	SEQ ID NO:8:	GYHWWRNWEY
25	SEQ ID NO:9:	KGFLWRARNW
	SEQ ID NO:10:	MNWKHWRARH
	SEQ ID NO:11:	FKWREWRGKL
	SEQ ID NO:12:	PDRQVRLWVR
	SEQ ID NO:13:	EVLRHWHPT
30	SEQ ID NO:14:	GPRVWMLNHG
	SEQ ID NO:15:	KKGRHHVTRV
	SEQ ID NO:16:	GGVCKCWQCL
	SEQ ID NO:17:	FSHSYGSAIR
	SEQ ID NO:18:	MHGHRRPGLA
35	SEQ ID NO:19:	MSKKPHLGLR
	SEQ ID NO:20:	TMWVELYSLK
	SEQ ID NO:21:	FVDPGRAGRG
	SEQ ID NO:23:	FRCCVFSCCLLS
	SEQ ID NO:24:	GFRCLVSLGGCF

SEQ ID NO:25: YSLWGLFVSDVV
SEQ ID NO:26: LFLWFNGAGFF
SEQ ID NO:27: VWGLFRGLENGS
SEQ ID NO:28: SLWRQWRGLFVV
5 SEQ ID NO:29: TLSLFGGRDKGF
SEQ ID NO:30: IGPAVSCLFRVC
SEQ ID NO:31: MSLEPLSPCLLI
SEQ ID NO:32: ALFSSVWGDVTL
SEQ ID NO:33: GWFGFEWVRGSC
10 SEQ ID NO:34: FWVSVGGVEGVV
SEQ ID NO:35: LGAFGGAGFLWR
SEQ ID NO:36: CRGIVFLFVGWL
SEQ ID NO:37: FWLVKGAGAWRF
SEQ ID NO:39: QVRLWARAGAGQ
15 SEQ ID NO:40: GLAVTEFGSVLEG
SEQ ID NO:41: VRWMCVIRLGVR
SEQ ID NO:42: RLWGFGVSRPVL
SEQ ID NO:43: CGSSLFRGPRCP
SEQ ID NO:44: LGISSLSFLQLR
20 SEQ ID NO:45: TWGWDGVSYLFL
SEQ ID NO:46: TRSLFDDFVSLR
SEQ ID NO:47: CYASLFRSRLCA
SEQ ID NO:48: DGSVRVWVRLI
SEQ ID NO:49: LSGFPVALVRFA
25 SEQ ID NO:50: LGGLLLVGSVFF
SEQ ID NO:51: VWARGVFRDRFF
SEQ ID NO:52: TGLLAGPVWRWT
SEQ ID NO:53: WLGGIFSCLVCG
SEQ ID NO:54: WFLRDVGGGSCS
30 SEQ ID NO:55: SRGCVFTWCSRS
SEQ ID NO:56: RCLVGYRCWGGV
SEQ ID NO:57: GFFCLVMGSSCA
SEQ ID NO:58: CGFDLVCARLEG
SEQ ID NO:59: DSGVRWFFGFLG
35 SEQ ID NO:60: ILDGCFFLGRCP
SEQ ID NO:61: CVRWLVSAAGCSG
SEQ ID NO:62: CVGCWLVCVLL
SEQ ID NO:63: CLFVFAAGFACG
SEQ ID NO:64: SCALEFGSCFST

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SEQ ID NO:65: CWGGVGVCGLLV
 SEQ ID NO:66: KRAWWKQKWV
 SEQ ID NO:67: CVGGVASRCQVL
 SEQ ID NO:68: SGAVLAGPFGVW
 5 SEQ ID NO:69: CRAFTDRVGVGVW
 SEQ ID NO:70: RCLVGYVVGGVW
 SEQ ID NO:71: VCLVYRSVDCWA
 SEQ ID NO:72: WRVVFVFTCVVWA
 SEQ ID NO:73: LWREWRGLFAVL
 10 SEQ ID NO:74: SGAVLAGPLWRL
 SEQ ID NO:75: FVVRGGTFLFVR
 SEQ ID NO:77: TGLLAGPVWRWT
 SEQ ID NO:78: DSGVRWFFGFLG
 SEQ ID NO:79: CAWHRLSFCGLV
 15 SEQ ID NO:80: CFGSALVLAVLA and
 SEQ ID NO:81: WFWDMSGEWGGL.

Most preferably, the peptide includes an amino acid sequence corresponding to consensus sequence
 20 SEQ ID NO: 38: WNWRYREYV.

Each of these peptides, represented by SEQ ID NOs 1 to 21, 23-37, 39-75 and 77-81, mimics the binding site within GPIb/IX for mab C-34. Mab C-34 thus binds to each of these peptides. However, the sequences of
 25 each of these peptides do not identify a continuous linear native sequence or necessarily occur at all within the sequence of any chain (i.e. GPIb alpha, GPIb beta, GPIX) of the GPIb/IX complex, thus the peptides are mimicking the mab C-34 binding site and are
 30 therefore mimotopes. The peptide of the subject invention also includes fragments of the above exemplified peptides which retain the ability to functionally mimic the binding site for a monoclonal antibody, such as C-34. The peptide having an amino
 35 acid sequence corresponding to SEQ ID NO:38 is an example of such a fragment, being a fragment of the peptide which includes the amino acid sequence corresponding to SEQ ID NO:1.

In another embodiment, the monoclonal antibody is designated SZ-1, and the peptide includes an amino acid sequence selected from the group consisting of:

5
SEQ ID NO:83: WHWRSSWKSG
SEQ ID NO:84: HRPLSWKGRA
SEQ ID NO:85: WHRRPMSWYS
SEQ ID NO:86: ARTKIWKPRW
10 SEQ ID NO:87: KRGWHWKSLL
SEQ ID NO:88: KKSWWVRMPR
SEQ ID NO:89: AKSWRYWRMP
SEQ ID NO:90: KRWKVYHRWP
SEQ ID NO:91: LHRWKQSPRT
15 SEQ ID NO:92: LIRWKPHGWR
SEQ ID NO:93: QKKFFSRWKH
SEQ ID NO:94: KWWVPRHRVW
SEQ ID NO:95: RSKWWVHRHS
SEQ ID NO:109: RWWHWVHRET
20 SEQ ID NO:110: KRWLWWANPR
SEQ ID NO:111: RHLWWGGRMK
SEQ ID NO:112: RLWFQHRGHR
SEQ ID NO:113: KRWHIRPTIR
SEQ ID NO:114: KRFKTHVHGR
25 SEQ ID NO:115: TKRFKRRHFL
SEQ ID NO:116: AKWHWHTRGR
SEQ ID NO:117: WHRHWGGFRI
SEQ ID NO:118: WHRNKPTWHS
SEQ ID NO:119: WHRAGVRAKV
30 SEQ ID NO:120: FKRFWHTGHR
SEQ ID NO:121: MMAWHARVAR
SEQ ID NO:122: WIWHRPIKVK
SEQ ID NO:123: WHRTLPRKRGH
SEQ ID NO:124: VKHFRWRPVA
35 SEQ ID NO:125: KRHWRFQLSN
SEQ ID NO:126: KRHRLASMAP
SEQ ID NO:127: WRWRWRGVLR
SEQ ID NO:128: RLHAHHARHR
SEQ ID NO:129: RWGAKHRVRV

SEQ ID NO:130: AMGWRFPVKHR
 SEQ ID NO:131: KWRWEMHQHY
 SEQ ID NO:132: WLSKLGHRHA
 SEQ ID NO:133: KHCSIHTRLR
 5 SEQ ID NO:134: GSAERMSEGH
 SEQ ID NO:135: FPLWNVLTMT
 SEQ ID NO:136: SFAGVGWFALLG
 SEQ ID NO:137: CILWVCFDGGG
 SEQ ID NO:138: LVARFPPPYGGV
 10 SEQ ID NO:139: SIVWLTRPKG
 SEQ ID NO:140: CRYPALNGVL
 SEQ ID NO:141: ALTSRTWARQ
 SEQ ID NO:142: TRYMLSRQSN
 SEQ ID NO:143: AMREARITVK
 15 SEQ ID NO:144: WRRHVPLRIL
 SEQ ID NO:145: FHRWNRPMVT
 SEQ ID NO:146: HRYKKTVPVM
 SEQ ID NO:147: WLHVKRRPVV
 SEQ ID NO:148: WVRHKHPIVP
 20 SEQ ID NO:149: LSMRRRQFQS
 SEQ ID NO:150: FHWRDKWRTG
 SEQ ID NO:151: RMRRPGITVK
 SEQ ID NO:152: GHRWNRPMVT
 SEQ ID NO:153: WRRHTPKRIP
 25 SEQ ID NO:154: WHWQRSRPAL
 SEQ ID NO:155: KRTWWHYIRP and
 SEQ ID NO:156: KRWRHSLPAS.

Each of these peptides, represented by SEQ ID
 30 NOs 83-93, 76, 82, and 109-156, mimics the binding site
 within GPIIb/IX for mab SZ-2. Mab SZ-2 thus binds to
 each of these peptides, which are referred to as
 mimotopes. The peptide of the subject invention also
 includes fragments of the above exemplified peptides
 35 which retain the ability to functionally mimic the
 binding site for monoclonal antibody SZ-2.

According to the subject invention, the
 monoclonal antibody (whose binding site is mimicked by
 the peptide of the invention, i.e. C-34 or SZ-2)

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recognizes an epitope within the human glycoprotein IIb/IIIa complex.

The invention also provides an isolated molecule capable of binding to the peptide. This isolated molecule is called an anti-mimotope. The anti-mimotope molecule can be any suitable molecule, such as, for example, an antibody, a second peptide, a carbohydrate, a DNA molecule, an RNA molecule, or a chemically synthesized molecule. Such peptides, proteins, or other biological, synthetic, or semi-synthetic molecules that are capable of binding to the mimotope can be identified by: raising antibodies against the mimotope; selecting from bacteriophage, chemical, hybridoma cell, or other types of libraries, cells, or chemical syntheses that might produce a set or subset of molecules having high affinity for the mimotope sequence; or designing molecules intended to have a high affinity for the mimotope sequences using computer-assisted or other theoretical approaches. Suitable anti-mimotopes can also be developed using in vitro evolution of nucleic acids capable of binding to the peptide mimotope (see Joyce 1994).

In one embodiment, the anti-mimotope of the subject invention constitutes a peptide which includes an amino acid sequence selected from the group consisting of:

SEQ ID NO:94: RHVAWWRQGV
30 SEQ ID NO:95: AKHRWWRRPV
SEQ ID NO:96: KHFMFHRHGV
SEQ ID NO:97: AGLNHWWKHK
SEQ ID NO:98: RRSTWHWWHA
SEQ ID NO:99: VAKWRHWNRRQ
35 SEQ ID NO:157: AYGVFHLGLS
SEQ ID NO:158: KKWGQHRQRS
SEQ ID NO:159: WRWMHWMPHA
SEQ ID NO:160: WHWLARHRTV
SEQ ID NO:161: RHRHRGFQPR

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SEQ ID NO:162: RGWRWHKYWQ
SEQ ID NO:163: KRHAWMESRL
SEQ ID NO:164: LLLVGGSELT
SEQ ID NO:165: KKVWMFSYNE
5 SEQ ID NO:166: LSCRGCPAFV
SEQ ID NO:167: HEGCEAQDEL
SEQ ID NO:168: SVRHIWFHVK
SEQ ID NO:169: GTWDLWRKGS
SEQ ID NO:170: RVLWPFVHKT
10 SEQ ID NO:171: HSPFRHVQPR and
SEQ ID NO:172: WVRGHHREVR.

These particular anti-mimotope peptides were generated to the mimotope which mimics the binding site for
15 monoclonal antibody C-34.

Such anti-mimotopes could serve as anti-thrombotic drugs. For example, the binding of mab C-34 to GPIb/IX inhibits ristocetin-induced aggregation of platelets. The mimotope peptide mimics the binding
20 site in GPIb/IX, and the anti-mimotope molecules bind to the mimotope peptide. Therefore, the anti-mimotopes, which could be peptides, should themselves complement the mimotope peptide. As such, the anti-mimotopes should be capable of binding to the original
25 epitope for mab C-34 or mab SZ-2 within the platelet glycoprotein Ib/IX complex, thereby inducing similar effects as does mab C-34 or mab SZ-2, i.e. the inhibition of ristocetin-induced aggregation of platelets that is dependent upon von Willebrand factor.

30 The invention thus provides a method of modulating the adhesion, aggregation, or agglutination of platelets, the method comprising selecting platelets and exposing the platelets to the anti-mimotope molecule of the subject invention. Such exposure
35 affects von Willebrand factor interaction with platelets through the glycoprotein Ib/IX receptor, thereby modulating the adhesion, aggregation, or agglutination of the platelets.

The invention also provides an isolated peptide capable of binding to monoclonal antibody 3-34 the peptide including an amino acid sequence selected from the group consisting of:

	SEQ ID NO:1:	AWNWEYREYV
	SEQ ID NO:2:	KWNWRNKKYV
	SEQ ID NO:3:	LSTWRYFEYV
	SEQ ID NO:4:	YLGWRYSEYV
10	SEQ ID NO:5:	TQMWEAREYL
	SEQ ID NO:6:	WEQREYWDPV
	SEQ ID NO:7:	EGSWPYRKGG
	SEQ ID NO:8:	GYHWRNWEY
	SEQ ID NO:9:	KGFLWFARNW
15	SEQ ID NO:10:	MNWKHWRARH
	SEQ ID NO:11:	FKWREWRGKL
	SEQ ID NO:12:	PDRQVRLWVF
	SEQ ID NO:13:	RVLRRHWHPR
	SEQ ID NO:14:	GRRVWMLNHS
20	SEQ ID NO:15:	KKGRHHVTRV
	SEQ ID NO:16:	GGVCHWQCL
	SEQ ID NO:17:	FSHSYCSAIR
	SEQ ID NO:18:	MHGHRRLSLA
	SEQ ID NO:19:	MSKKPHLSLR
25	SEQ ID NO:20:	TMWVELYSLE
	SEQ ID NO:21:	FVDFGRAGRG
	SEQ ID NO:22:	FRCCVFSCLLS
	SEQ ID NO:23:	GFRCLVSLGGCF
	SEQ ID NO:24:	YSLWGLPVGDVV
30	SEQ ID NO:25:	LPDLLWFNGAGFF
	SEQ ID NO:26:	VWGLFRGLENGS
	SEQ ID NO:27:	SLWRQWRGLFVV
	SEQ ID NO:28:	TLSLFGGREDKGF
	SEQ ID NO:29:	IGPAVSCLFRVC
35	SEQ ID NO:30:	MSLFPLSFCRLI
	SEQ ID NO:31:	ALFSSWGEVTL
	SEQ ID NO:32:	GWFGPFWVRSSG
	SEQ ID NO:33:	FWVSVGGVEGVV
	SEQ ID NO:34:	LGAFGGAGFLWR

SEQ ID NO:36: CRGIVFLFVGWL
SEQ ID NO:37: FWLVKGAGAWRF
SEQ ID NO:38: QVRLWARAGASQ
SEQ ID NO:39: GLAVTFGSVLEG
5 SEQ ID NO:40: VAWMCVIRLGVR
SEQ ID NO:41: RLWGPGVSRPVL
SEQ ID NO:42: CGSSLFRGPRCP
SEQ ID NO:43: LBISSLSFLQLR
SEQ ID NO:44: TWGWDGVSYLEL
10 SEQ ID NO:45: TRSLFDDFVSLR
SEQ ID NO:46: QYASLFRSRLCA
SEQ ID NO:47: DGSVRVWVRLL
SEQ ID NO:48: LSGFPVALVRFA
SEQ ID NO:49: LGGGLLVGSVFP
15 SEQ ID NO:50: VWARGVFEDRFF
SEQ ID NO:51: TGLLAGPVWRWT
SEQ ID NO:52: WLGGI FSCLVCG
SEQ ID NO:53: WFLRDVCGCSCL
SEQ ID NO:54: SRCGVFTWCERS
20 SEQ ID NO:55: RCLVGYRCWGGV
SEQ ID NO:56: GFRCLVMGGGCA
SEQ ID NO:57: CGFDLVCARLEG
SEQ ID NO:58: DSGVRWFFGFLG
SEQ ID NO:59: ILDGCFFLGRCP
25 SEQ ID NO:60: EVRWLVSA GCSG
SEQ ID NO:61: EVGCWLVC DVLL
SEQ ID NO:62: CLFVFAAGFACG
SEQ ID NO:63: SCALFGSCFGIS
SEQ ID NO:64: CWGGVGVCGLLV
30 SEQ ID NO:65: KFAWWKQKWV
SEQ ID NO:66: CVGGVASRCGVL
SEQ ID NO:67: SGAVLAGPFGVW
SEQ ID NO:68: CRAFD RVGV CVW
SEQ ID NO:69: RCLVGYVVG SVW
35 SEQ ID NO:70: VCLVYRSVDCWA
SEQ ID NO:71: WRVFVFTCVVWA
SEQ ID NO:72: LWREWRGLFAVL
SEQ ID NO:73: SGAVLAGPLWRL
SEQ ID NO:74: FVVRGGTFLFVR

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SEQ ID NO:77: TGLLAGFVWRWT
SEQ ID NO:78: DSGVRWFFGFLG
SEQ ID NO:79: CAWHRLSFCGLV
SEQ ID NO:80: CFCSALVLAVLA and
5 SEQ ID NO:81: WFWDYSSGEWGGI.

Further provided is a fragment of any of the above peptides wherein the fragment retains the ability to bind to monoclonal antibody C-34. Such a fragment
10 is exemplified by SEQ ID NO:36, which is a fragment of SEQ ID NO:1.

The invention also provides an isolated molecule capable of binding to the above peptides, also known as an anti mimotope. Suitable molecules include
15 an antibody, another peptide, a DNA or RNA molecule, a carbohydrate, or a chemically synthesized molecule.

As above, the invention thus provides a method of modulating the adhesion, aggregation, or agglutination of platelets, the method comprising
20 selecting platelets and exposing the platelets to the anti-mimotope molecule. Such exposure affects von Willebrand factor interaction with platelets through the glycoprotein IIb/III receptor, thereby modulating the adhesion, aggregation, or agglutination of the
25 platelets.

In one preferred embodiment, the invention provides an isolated peptide capable of binding to monoclonal antibody C-34 and including an amino acid sequence corresponding to SEQ ID NO:38: WNWRYREYV.

30 The invention further provides an isolated peptide capable of binding to monoclonal antibody 57-2, the peptide including an amino acid sequence selected from the group consisting of:

35 SEQ ID NO:83: WHWRSSWKSG
SEQ ID NO:84: HRPLSWKGRA
SEQ ID NO:85: WHRRPMSWYS
SEQ ID NO:86: ARIKIWKPRW
SEQ ID NO:87: KRGWHWKS LH

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SEQ ID NO:88: KKSWWVRMPR
SEQ ID NO:89: AKSWRYWRMP
SEQ ID NO:90: KRWKVYHRWF
SEQ ID NO:91: LHRWKQSPRT
5 SEQ ID NO:92: LIRWKPHGWF
SEQ ID NO:93: QKKFFSRWKH
SEQ ID NO:76: KWWVPRHRVW
SEQ ID NO:82: RSKWWVHRHS
SEQ ID NO:109: RWWHWVHFET
10 SEQ ID NO:110: KRWLWWANPR
SEQ ID NO:111: RHLWWGGRMK
SEQ ID NO:112: RLWPQHRGHR
SEQ ID NO:113: KRWHIRPTIR
SEQ ID NO:114: KRFKTHVHGE
15 SEQ ID NO:115: TKRFKHRHFL
SEQ ID NO:116: AKWHWHTRGR
SEQ ID NO:117: WHRHWWGGFRI
SEQ ID NO:118: WHRNKPTWHS
SEQ ID NO:119: WHRAGVPAKV
20 SEQ ID NO:120: FKRFWHTGHE
SEQ ID NO:121: MMAWHARVAR
SEQ ID NO:122: WIWHRPIKVK
SEQ ID NO:123: WHRTLPRGRH
SEQ ID NO:124: VKHFFRWPVA
25 SEQ ID NO:125: KRHWRFQLSN
SEQ ID NO:126: KRHRLASMAP
SEQ ID NO:127: WRWRWRGVLR
SEQ ID NO:128: RLHAHHARHR
SEQ ID NO:129: RWGAKHRVFW
30 SEQ ID NO:130: AMGWRPVKHR
SEQ ID NO:131: KWRWRMHQHY
SEQ ID NO:132: WLSKLGHRHA
SEQ ID NO:133: KHCSIHTRLR
SEQ ID NO:134: GSAERMSEGH
35 SEQ ID NO:135: FPLWNVLTMT
SEQ ID NO:136: SFAGVGWFALLG
SEQ ID NO:137: CDLWVCFLDGGG
SEQ ID NO:138: LVARFPPPYGGV
SEQ ID NO:139: SIVWLTRPKG

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SEQ ID NO:141: CRYRALNGVL
SEQ ID NO:142: ALTSRTWARQ
SEQ ID NO:143: TRYMLSRQSN
SEQ ID NO:144: AMREARITVK
5 SEQ ID NO:145: WRRHNVPLRIL
SEQ ID NO:146: FHRWNRPMVT
SEQ ID NO:147: HRYKKTPVPM
SEQ ID NO:148: WLHVKKRRPVV
SEQ ID NO:149: LSMRRRQFQS
10 SEQ ID NO:150: FHWKFKWRTG
SEQ ID NO:151: RMRRPGITVK
SEQ ID NO:152: GHRWNRPMVT
SEQ ID NO:153: WRRHTPKRIH
15 SEQ ID NO:154: WHWQSRPAL
SEQ ID NO:155: KRTWWHYIRP and
SEQ ID NO:156: KRWRHSLPAS.

20 Further provided is a fragment of any of the above peptides wherein the fragment retains the ability to bind to monoclonal antibody SZ-3. The invention also provides an isolated molecule capable of binding to the above peptides (an anti-mimotope), and a method
25 of modulating the adhesion, aggregation or agglutination of platelets by exposing the platelets to the anti-mimotope molecule.

The invention is described in further detail as follows.

30

The C-34 Epitope

As reported by Miller, et al. (1990), platelets from patients with platelet-type von Willebrand disease (PT-vWD) heterozygous for the
35 mutation 230•WKQ(G→V)₂₃₃V•234 in the alpha chain of platelet glycoprotein Ib were used as immunogens for the production of murine mabs. One such mab, C-34, inhibited ristocetin-induced aggregation of patient or normal platelets, but not aggregation induced by other

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aggregating agents. As demonstrated by crossed-immunoelectrophoresis, mab C-34 recognized an epitope within the GPIb/IX complex. In indirect immunofluorescence studies on fresh platelets, the ratio of any of four different anti-GPIb mabs to one another was near unity (0.88-1.14) both for normals and for patients. In contrast, the ratio of the binding of mab C-34 to such a mab (AP-1) was 0.31 ± 0.02 (means \pm SE, for normal platelets and significantly increased to 0.54 ± 0.01 for patient platelets ($p < 0.001$). In immunoprecipitations on NP-40 lysates of 3H -labeled platelets, saturating concentrations of mab C-34 produced much fainter bands than did AS-2 or other anti-GPIb mabs. In contrast to the other anti-GPIb mabs, C-34 did not bind to the purified ^{125}I -labeled glyccocalicin fragment of GPIb or to the glyccocalicin derivative identified by crossed-immunoelectrophoresis. In immunoprecipitation studies of 3H -labeled platelets subjected to digestion with trypsin or with chymotrypsin, C-34 identified neither the glyccocalicin nor the amino-terminal 45 kDa fragment of GPIb alpha that were immunoprecipitated by mab AS-2 or by mab AS-7.

Thus, using three independent techniques (immunoprecipitation of platelet glycoproteins following radiolabeling of intact platelets and subsequent proteolytic digestion of these glycoproteins; immunoprecipitation of radiolabeled purified glyccocalicin; crossed immunoelectrophoresis of platelet glycoproteins) (Miller et al. 1990), it has been shown that while C-34 recognizes an epitope within the GPIb/IX complex, this epitope does not appear to reside within glyccocalicin.

While these studies reported a relatively simple method that succeeded in epitope mapping mabs AS 2 and AS 7 to the 45 kDa region of GPIb alpha, this work demonstrated that mab C-34 cannot be mapped to any single tryptic or chymotryptic domain of glyccocalicin. Additionally, mab C-34 does not produce

immunoprecipitation patterns similar to those of a mab recognizing GPIX.

Biopanning of Mab C-34 With Bacteriophage Display Libraries

Scott and Smith (1990) presented a method of defining peptide ligands by using randomly synthesized peptide inserts in bacteriophage. Related methods were published by Gwirla et al. (1990) and by Devlin et al. (1990). Since that time a literature has arisen in which both the original hexapeptide inserts and larger inserts have been used in identifying epitopes recognized by monoclonal antibodies. This technique has great potential for the detection of critical epitopes within the platelet vWF receptor known as GPIb/IX. The studies disclosed herein focus on monoclonal antibody C-34, but can be applied to other monoclonal antibodies having binding sites (epitopes) within GPIb/IX by the methods disclosed herein for mab C-34.

A well-balanced decapeptide (10-mer) library from Dr. Bruce Malcom of Alberta, Canada (described by Christian et al. 1992), and a dodecapeptide (12-mer) library from Clontech Laboratories (Palo Alto, CA) were used. In the dodecapeptide library, a reduced frequency of adenosines at the first two positions of each codon causes a characteristic underrepresentation of the following amino acids indicated by their one-letter codes: I, M, T, N, K, Y, H, Q, D, and E. The libraries have both been constructed into a Fuse 5 vector (Scott and Smith 1990) by the insertion of a mixture of synthetic oligonucleotides, with the random decapeptides (or modified-random dodecapeptides) fused to the minor viral coat protein pIII of the bacteriophage. The libraries each have a complexity of approximately 3×10^8 independent clones, and a titer of 10^8 to 10^9 per ml. While the Malcom library constitutes only a partial decapeptide library, it is complete as a hexapeptide library.

The strategy for using these libraries largely follows the review recently presented by Scott (1992) and employs, with modifications, the detailed methodology for use of this system as described recently by Smith and Scott (1993). The strategy used herein is as follows.

Specifically, in the first round of biopanning a 60 mm streptavidin-coated petri dish is filled with blocking solution (0.5% BSA, 0.1 M NaHCO₃, 0.1 µg/ml streptavidin, 0.2% NaN₃) for 2 hours, then washed three times with TBS-0.5% Tween. Next, 1 µl of the library (about 1×10^{12} phage) that has been incubated overnight at 4°C with 1 µg of biotinylated Mab is diluted with 1 ml of TBS Tween, and this mixture is then added to the petri dish and rocked for 15 minutes at room temperature. The petri dish is washed 10 times with TBS-Tween, and bound phage is eluted by pipetting 800 µl of 0.1 N HCl (pH adjusted to 2.2 with glycine) - 1 mg/ml BSA into the dish. The eluate is then pipetted into a microfuge tube containing 48 µl of 2M Tris, to bring the pH up to about 8.

The eluate is concentrated and washed twice in TBS using an Amicon Centricon-30 filter (Amicon, Inc., Beverly, MA). This final product is titered out by making dilutions from a small amount of concentrated eluate in TBS-0.1% gelatin and adding 1 µl of each dilution made to 19 µl of TBS-gelatin, then adding 20 µl of starved K91 *E. coli* cells and incubating for 10 minutes at room temperature. After adding 200 µl of NZY medium containing 0.2 µg/ml tetracycline (Tc) and incubating at 37°C for 1 hour, the mixture is plated out on NZY agar plates containing 40 µg/ml tetracycline and allowed to grow up overnight at 37°C.

After titering, the entire concentrated eluate from the first round of biopanning (about 50 µl) is added to an equal volume of fresh starved K91 cells, and amplification performed as described by Smith and Scott (1993). Following the first PEG/NaCl precipitation, the resulting pellet is dissolved in 1

ml TBS. Phage is then precipitated a second time with
PEG/NaCl, allowed to stand at least 1 hour at 4°C, and
the precipitate collected following centrifugation at
4°C. After careful removal of all the supernatant, the
5 pellet is dissolved in 100 µl TBS. This amplified
product can then be titered.

The first round of biopanning results in a
yield of $5 \times 10^{-4}\%$. The second biopanning also used 1 µg
of biotinylated C-34 with 1×10^{10} phage, resulting in a
10 yield of $4 \times 10^{-4}\%$. The second round of biopanning is
concentrated and amplified as in the first round. In
the third round, 0.01 µg of biotinylated C-34 was
biopanned against 2.5×10^{10} phage, with a resulting yield
of $3 \times 10^{-4}\%$. The third round is stopped after eluting
15 the bound phage from the petri dish. This eluate is
not concentrated or amplified. Titerings are done
before and after each round, and the percent yield is
calculated as the number of bacteriophage obtained in
an elution fraction relative to the initial number of
20 bacteriophage (Christian et al. 1992). A yield should
generally be greater than 10^{-5} to exceed background,
with values of 10^{-4} to 10^{-3} typically observed.
Increasing percent yields in subsequent rounds of
biopanning are, in particular, suggestive that clones
25 of increasing affinity are being selected.

For studies directed towards discovering a
peptide binding the mimotope peptide (SEQ ID NO:1:
AWNWRVREYV), two rounds of biopanning against the
original decapeptide library were performed, using 1 µg
30 of biotinylated mimotope peptide in the first round and
0.01 µg in the second round. Resulting yields were
 $3 \times 10^{-4}\%$ and $2 \times 10^{-3}\%$, respectively.

In some experiments, an immunological
screening assay, as described by Christian, et al.
35 (1992) may be performed using NZY + Tc agar plates
containing about 500 well-separated colonies. The
colonies are transferred to nitrocellulose membrane
filters (Biorad Laboratories, Hercules, CA), and the
filters are immediately washed twice in TNT Buffer (10

5 mM Tris, pH 8.0, 150 mM NaCl, 0.05% Tween 20, blocked for 30 minutes at room temperature with gentle agitation in 20% normal goat serum in TNT buffer, then incubated for 2 hours at room temperature in primary
10 mab that has been diluted 1:1000 in blocking buffer. The filters are washed sequentially for 10 minutes at room temperature each wash, in washing buffer A (TNT Buffer + 0.1% BSA), washing buffer B (TNT Buffer + 0.1% BSA + 0.1% NP-40), and then again washing buffer A, and
15 incubated in a secondary peroxidase-conjugated goat anti-mouse IgG for 1-1/2 hours at room temperature. The filters are washed as before, then put in a final wash of TN (10 mM Tris, pH. 7.5, 150 mM NaCl). Color development is observed after putting filters in ABTS substrate.

Small cultures of individual colonies are then grown up overnight, by either: a) selecting the colonies that were positive from the immunological screening; or b) skipping the screening step and
20 randomly selecting colonies (about 100). Each colony is inoculated into 2 ml of NZY medium containing 20 µg/ml tetracycline, and these small cultures grown up overnight at 37°C, with vigorous shaking. The next day cultures are centrifuged to pellet the cells, and the
25 supernatant is removed. To 1 ml of the supernatant is then added 150 µl PEG/NaCl, and the phage are precipitated overnight at 4°C. Following subsequent centrifugation and removal of supernatant, the pellet is dissolved in 1 ml TBS.

30 For DNA sequencing, 400 µl of the dissolved pellet is extracted once with phenol, and the resulting aqueous phase (about 300 µl) is added to 500 µl TE and 80 µl 3M sodium acetate buffer. Then 1 ml ethanol is added and the SS DNA is allowed to precipitate
35 overnight at 4°C. Each sample is then microfuged for 30 minutes at 4°C, the DNA pellet washed once in 70% ETOH, dried, and resuspended in 7 µl H₂O. This template can be stored at -20°C until ready to use.

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Due to the quite GC-rich Sfi I cloning site flanking the insertion region (Christian et al., 1992), sequencing reactions are carried out using the Sequenase 2-deaza dGTP DNA sequencing kit (Amersham-US Biochemicals, Arlington Heights, IL) with ³²P-dATP and an antisense primer located approximately 40 nucleotides 3' to the insert site (primer having SEQ ID NO:100: 5' CTCATAGTTAGCGTAACG-3'). Samples are run on a standard 6% sequencing gel using an ABI 373A sequencing apparatus (Eastman Kodak Company, Rochester, NY).

The GCG software (Genetics Computer Group, Inc., Madison WI) is helpful for aligning sequences obtained from multiple clones in order to find consensus sequences. Certainly in the case of new maps for which binding sites are sought, but even in the case of mab C-34, there is an interest in searching for sequences not only in GPIb alpha, but also in GPIb beta, GPIX, and in fact other platelet proteins that have been deposited in the available databases (Swiss Prot, Gen Bank, EMBL, etc.). Indeed, this analysis may provide important new information suggesting that a particular monoclonal antibody's epitope may be comprised of multiple components of the GPIb/IX complex that must accordingly be in close spatial proximity.

At this point, an ELISA assay can be used to evaluate individual clones, if the number of clones is high. In brief, phage having undergone two PEG precipitations, and subsequently adjusted for titer, can be incubated overnight with biotinylated mab, following which the mab-phage mixture can be added to wells of microtiter plates that have been previously coated with formalin-fixed platelets (or other suitable immobilized target recognized by the mab). Following a series of washing steps, avidin-peroxidase is added, the wells washed again, chromogenic substrate added, and the wells eventually read on an ELISA plate reader. The relative decrease in strength of signal in this assay provides guidance as to the most promising clones

for further study. Consensus peptides identified in this manner can be chemically synthesized and characterized with respect to ability to bind original antibody. Peptides showing high binding affinity for the antibody can then be used as immunogens in mice and or rabbits.

Epitope Mapping Studies of mab C-34

The two phage display libraries discussed above were employed in mapping studies with mab C-34. Results with the balanced, 10-mer peptide library were quite definitive with respect to strong consensus development among clones selected after two or three rounds of biopanning. Not only is there an evident consensus towards the 9-mer sequence SEQ ID NO: 38: W N W R Y R E Y V, but the 10-mer peptide including this sequence (SEQ ID NO: 1) with an amino terminal alanine appeared to have the greatest selective advantage in the biopanning, since clones bearing this sequence were found the most frequently.

The series of cloned sequences is included in alignment form below. Double-underlines represent consensus amino acids and single-underlined amino acids represent significant homology to the consensus.

			<u>Frequency</u>
	C34 Clone SEQ ID NO:1:	.A <u>W</u> N <u>W</u> R <u>Y</u> R <u>E</u> YV	52
	C34 Clone SEQ ID NO:2:	.K <u>W</u> N <u>W</u> R <u>N</u> K <u>K</u> YV	1
	C34 Clone SEQ ID NO:3:	.L <u>S</u> T <u>W</u> R <u>Y</u> F <u>E</u> YV	14
30	C34 Clone SEQ ID NO:4:	.Y <u>L</u> G <u>W</u> R <u>Y</u> S <u>E</u> YV	7
	C34 Clone SEQ ID NO:5:	.T <u>Q</u> M <u>W</u> R <u>E</u> A <u>R</u> E <u>Y</u> L	2
	C34 Clone SEQ ID NO:6:	... <u>W</u> E <u>Q</u> R <u>E</u> Y <u>W</u> D <u>P</u> V	1
	C34 Clone SEQ ID NO:7:	.E <u>G</u> S <u>W</u> R <u>Y</u> R <u>K</u> G <u>G</u>	1
	C34 Clone SEQ ID NO:8:	G <u>Y</u> H <u>W</u> <u>W</u> R <u>N</u> W <u>E</u> Y	2
35	C34 Clone SEQ ID NO:9:	K <u>G</u> E <u>L</u> <u>W</u> E <u>A</u> R <u>N</u> W	1
	C34 Clone SEQ ID NO:10:	M <u>N</u> W <u>K</u> H <u>W</u> P <u>A</u> R <u>H</u> .	1
	C34 Clone SEQ ID NO:11:	<u>F</u> K <u>W</u> R <u>E</u> W <u>R</u> G <u>K</u> L	1
	C34 Clone SEQ ID NO:12:	.P <u>D</u> E <u>Q</u> V <u>R</u> L <u>W</u> V <u>R</u>	1
	C34 Clone SEQ ID NO:13:	<u>E</u> V <u>L</u> R <u>H</u> W <u>H</u> P <u>R</u> T	1

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	C34 Clone SEQ ID NO:14:	. <u>GRE</u> <u>V</u> WMLNHS	2
	C34 Clone SEQ ID NO:15:	. <u>KY</u> <u>GE</u> <u>HHY</u> TRV	22
	C34 Clone SEQ ID NO:16:	.GSVCKCWQCL	1
	C34 Clone SEQ ID NO:17:	FSHSYGSAIR	1
5	C34 Clone SEQ ID NO:18:	MHGHRREFLA	1
	C34 Clone SEQ ID NO:19:	MSKKPHLGSR	1
	C34 Clone SEQ ID NO:20:	TMWVELYSLE	1
	C34 Clone SEQ ID NO:21:	FVPPSPASRG	1
	C34 Clone SEQ ID NO:66:	KRAWKQFWV	1

10

Results with the second peptide display library that is partially restricted in its amino acid repertoire revealed a series of clones which bind to C-34 without any appearance of the minotope consensus sequence SEQ ID NO:38. The series of cloned sequences from the second library is included in alignment form below. SEQ ID NO:22 is the native sequence of GPIb alpha from amino acid 484 to 498, and represents a possible natural epitope sequence revealed by the clones isolated from the second library. The ' represents potential chymotrypsin cleavage sites. As above, double-underlines represent the possible native sequence SEQ ID NO:22 within this second library and single underlined amino acids represent significant homology to the possible native sequence.

15
20
25

C34b series versus GPIb 484-499

SEQ ID NO:22:

C C L L P L G P Y V L G L P W L

SEQ ID NO:23:

P R C C V F S C C L L S

SEQ ID NO:24:

G F R C L V S L G G C P

SEQ ID NO:25:

Y S L W G L P V G D V V

SEQ ID NO:26:

L P L L W E N G A G F E

SEQ ID NO:27:

V W G L F R G L E N G S

SEQ ID NO:28:

S L W R Q W R G L F V V

SEQ ID NO:29:

T L S L E G G R D K G F

SEQ ID NO:30:

I G P A V S C L F R V C

SEQ ID NO:31:

M S L F P L S F C R L I

SEQ ID NO:32:

A L F S S V W G D V T L

SEQ ID NO:33:

G W F G P F W V R G S G

SEQ ID NO:34:

F W V S V G G V E G V V

SEQ ID NO:35:

L G A F G G A G F L W R

SEQ ID NO:36:

C R G I V F L F V G W L

SEQ ID NO:37:

F W L V K G A G A W R F

* = Potential Chymotrypsin Cleavage Site

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The following cloned sequences were also obtained from the second peptide display library:

	SEQ ID NO:39:	QVRLWARAGAGQ
5	SEQ ID NO:40:	GLAVTFGSSVLEG
	SEQ ID NO:41:	VRWMCVIRLGVR
	SEQ ID NO:42:	RLWGPGVSRPVL
	SEQ ID NO:43:	CGSSLFRRGPRCP
	SEQ ID NO:44:	LGISSLSFLQLR
10	SEQ ID NO:45:	TWGWDGVSYLEL
	SEQ ID NO:46:	TRSLFDIEFVSLR
	SEQ ID NO:47:	CYASLFRRRLCA
	SEQ ID NO:48:	DGSVRVWVRLL
	SEQ ID NO:49:	LSGFPVALVRFA
15	SEQ ID NO:50:	LGGGLLVGSVFF
	SEQ ID NO:51:	VWARGVFRDRFF
	SEQ ID NO:52:	TGLLAGFVWRWT
	SEQ ID NO:53:	WLGGFSCLVCG
	SEQ ID NO:54:	WFLRDVGCSSCL
20	SEQ ID NO:55:	SRGCVFTWCSRS
	SEQ ID NO:56:	RCLVGYRCWGGV
	SEQ ID NO:57:	GFRCLVMGGGA
	SEQ ID NO:58:	CGFDLVCARLFQ
	SEQ ID NO:59:	DSGVRWFFGFLQ
25	SEQ ID NO:60:	ILDGCFELGRCP
	SEQ ID NO:61:	QVRWLVSAGCSG
	SEQ ID NO:62:	CVGCWLVCDEVL
	SEQ ID NO:63:	CLFVFAAGFACG
	SEQ ID NO:64:	SCALFGSCFGIS
30	SEQ ID NO:65:	CWGGVGVCGLLV
	SEQ ID NO:67:	CVGGVASRCGVL
	SEQ ID NO:68:	SGAVLAGPFGVW
	SEQ ID NO:69:	CRAFDRVGVCVW
	SEQ ID NO:70:	RCLVGYVVGCVW
35	SEQ ID NO:71:	VCLVYRSVDQWA
	SEQ ID NO:72:	WRVFVFTCVVWA
	SEQ ID NO:73:	LWREWRLFAVL
	SEQ ID NO:74:	SGAVLAGPLWRL
	SEQ ID NO:75:	FVVRGGTFLEVR

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SEQ ID NO:77: TGLLASPVWRWT
SEQ ID NO:78: DSGVRWFFGFLG
SEQ ID NO:79: CAWHRLSFCGLV
SEQ ID NO:80: CFGSALVLAVLA and
5 SEQ ID NO:81: WFWDMSGEWGGL.

Comparison of Consensus Sequence to Native Sequences

Considerable effort was extended in trying to relate the consensus sequence of the above peptide (SEQ ID NO:38) to native sequences within GPIb alpha or other known proteins in the Swiss Protein or NCBI data banks. No such relation was found. This sequence accordingly represents a "mimotope" - i.e., a peptide which mimics a native epitope (a binding site for a monoclonal antibody), despite a lack of apparent homology at the primary amino acid sequence level (for mimotopes, see: Motti et al. 1994, Larocca et al. 1992, Lenstra et al. 1992, Balass et al. 1993, Hobart et al. 1993, and Luzzago et al. 1993). As noted after reviewing SEQ ID NOs: 1-21 and 66 above, not all selected clones appear to be part of this consensus group, and it is possible that with further sequencing clues as to the native epitope may be derived.

By using the second peptide display library that is partially restricted in its amino acid repertoire, another series of clones ("C34b" series) binding to C-34 without appearance of the mimotope consensus peptides were obtained. Following sequencing of these clones, a FASTA analysis (Pearson and Lipman 1988; Pearson 1990) was performed upon this group of clones by moving a 7-amino acid window along the sequence of GPIb alpha, advancing one amino acid at a time, and determining the group score as a function of position in the GPIb alpha molecule.

The results do not, in general, offer compelling matches in the sense of consensus development among the clones. However, the possible native GPIb alpha sequence revealed by this analysis is represented by SEQ ID NO:22.

Aggregation Studies

Citrated human platelet-rich plasma (PRP) was prepared by standard methods (Miller et al. 1983). For study of C-34 neutralization by mimotope peptide, 350 μ L of PRP containing 150,000 platelets/ μ L was incubated for 10 min at 22°C with phosphate-buffered saline (PBS), 20 μ g/mL C-34 mab, or 20 μ g/mL C-34 that had previously been incubated for 30 min at 22°C with varying concentrations of peptides. The PRP was then brought to 37°C and stirred at 1000 rpm in a Chrono-Log lumi-aggregometer (Chrono-Log Corporation, Havertown, PA). Aggregation was initiated by the addition of 1 mg/mL ristocetin (Helena Laboratories, Beaumont, TX). For screening of bacteriophage clones displaying potential anti-mimotope peptides, 150 μ L of PEG/NaCl precipitated phage was incubated with 250 μ L of citrated PRP for one hour at 22°C, transferred to the aggregometer, following which ristocetin was added at a final concentration of 0.8 mg/mL. Study of the inhibitory potency of synthetic peptides upon vWF-dependent platelet aggregation was performed by pre-incubating 150 μ L of varying dilutions of peptide dissolved in PBS, pH 6.0 for 2-4 hr at 22°C with 250 μ L of formalin-fixed (Macfarlane et al. 1975) platelets (1.5×10^6 /mL), following which the mixture was warmed to 37°C in the aggregometer, purified vWF (Miller et al. 1983) (1 U/mL) was added, and aggregation was initiated by the addition of 0.8 mg/mL ristocetin.

Synthesized Peptide

A peptide including the consensus sequence (SEQ ID NO: 38) was chemically synthesized (Genosys Biotechnologies, The Woodlands, Texas). The synthesized peptide had an amino acid sequence corresponding to SEQ ID NO:1: AWWNRYREYV. A modification of this peptide with a biotin attached to the amino-terminal alanine (N-hydroxysuccinimide hexanoic acid long chain spacer arm biotinylation) was also synthesized. One mg of the chemically synthesized

biotinylated peptide was dissolved in one ml of water containing 20 μ l of DMSO. Since C-34 at a final concentration of 20 μ g/mL is a potent inhibitor of ristocetin-induced aggregation in citrated platelet-rich plasma (PRP), the synthetic peptide's potency was assessed by examining whether the peptide could neutralize the inhibitory activity of C-34 in this setting. Accordingly, approximately 10 μ g of C-34 was incubated at 22°C for 30 minutes with varying concentrations of test or control peptide, following which the mixture was added to PRP in a final volume of approximately 0.5 ml for an additional 10 minutes at 22°C. As can be seen from the resulting aggregation curves (Figures 1-7), the synthesized peptide fully neutralized the C-34, producing half-maximal neutralization of the C-34 at about 1.0 μ g/ml, which is approximately 0.55 μ M for the biotinylated peptide. A similar pattern of C-34 antibody neutralization was observed when the non-biotinylated form of the peptide (having SEQ ID NO:38) was used, with half-maximal neutralization at approximately 3.0 μ M. The peptide (native or biotinylated) by itself did not induce platelet aggregation, nor did it appear to have non-specific effects, inasmuch as it had no influence on ADP-induced aggregation.

More specifically, Fig. 1 shows the ristocetin-induced full aggregation of platelets in the presence of von Willebrand factor. Fig. 2 shows the inhibition of ristocetin-induced aggregation of platelets by 20 μ g/ml of mab C-34. Figs. 3-7 show varying degrees of neutralization of the inhibition of ristocetin-induced aggregation of platelets by 20 μ g/ml of mab C-34 in the presence of 0.14, 0.27, 0.55, 1.1, and 2.3 μ M of the synthetic biotinylated peptide mimotope having SEQ ID NO:1, respectively. In Fig. 3, 0.14 μ M of the peptide does not neutralize the C-34 inhibition; in Fig. 7, 2.3 μ M of the peptide fully neutralizes the C-34 inhibition, and Figs. 4-6 show

varying degrees of neutralization of the C-34 inhibition.

Additional Use of Synthesized Peptide

5 The chemically synthesized peptide can be conjugated to bovine serum albumin and used for raising polyclonal antibodies in rabbits. Standard procedures can be used to immunize the rabbits and to collect serum, as described below. Polyclonal antibody can be
10 tested for its ability to bind to normal platelets, as well as to the wild-type and valine 233 mutant forms of recombinant GPIb alpha. For polyclonal antibody that shows a high affinity binding to platelets, functional studies can then be undertaken. These studies include
15 adhesion, aggregation, agglutination, and vWF binding. F(ab)'₂ and Fab fragments of the polyclonal antibody can be made if steric hindrance appears to be preventing an accurate evaluation of more specific modulating effects of the antibody (Becker and Miller 1989, Kupinski and
20 Miller 1986, and Miller et al. 1986). Polyclonal antibody to the synthetic peptide that recognizes or stabilizes a conformation associated with heightened or diminished affinity for binding vWF can be obtained at
25 a 95% purity and conjugated to bovine serum albumin or to another carrier protein, for the production of murine monoclonal antibodies.

Production of Antibodies to Synthesized Peptides

 Mice: Monoclonal antibody production can be
30 carried out using BALB/c mice. Immunization of the B-cell donor mice can involve immunizing them with antigens mixed in TiterMax™ adjuvant as follows: 50 µg antigen/20 µl emulsion x 2 injections given by an intramuscular injection in each hind flank on day 1.
35 Blood samples can be drawn by tail bleeds on days 28 and 56 to check the titers by ELISA assay. At peak titer (usually day 56) the mice can be subjected to euthanasia by CO₂ inhalation, after which splenectomies

can be performed and spleen cells harvested for the preparation of hybridomas by standard methods.

Rabbits: Polyclonal antibodies can be raised in New Zealand white rabbits. Preimmune serum can be collected from rabbits sedated with ketamine/rompun ketamine HCl at 20 mg/kg IM and xylazine HCl at 4 mg/kg IM) via the auricular artery. Ten to fifteen percent of the total blood volume can be collected at each bleeding. The hair over the ear can be shaved with a #40 clipper blade, wiped with 70% alcohol, and a sterile 22 gauge butterfly can be used for blood collection. The antigen can be mixed with either RIBI adjuvant or TITER-MAX™ adjuvant and used according to the manufacturer's instructions. The back can then be shaved, wiped with 70% alcohol, and a sterile 25 gauge needle with the antigen/adjuvant mixture therein can be used to administer subcutaneously and intramuscularly as recommended by the manufacturer's instructions. Immune serum samples can be collected as described for preimmune samples. When sufficient titers are reached, the animal can be anesthetized with sodium pentobarbital (60 mg/kg BW) via the lateral ear vein until deep anesthesia is achieved. Blood can be immediately collected via cardiac puncture into plastic centrifuge tubes and allowed to clot; afterwards, the blood can be centrifuged and the serum aspirated and frozen at -70° C. For euthanasia, while under sodium pentobarbital anesthesia at a dosage of 60 mg/kg, the rabbit can be exsanguinated via cardiac puncture.

30

Development of C-34 Anti-Mimotope Peptides

The mimotope decapeptide itself was then used as a probe to search for "anti-mimotope" peptides. Specifically, while a number of peptides might interact with some portion of the mimotope peptide exposed in solution, an "anti-mimotope" peptide would be defined as one that was not only selected in multiple rounds of biopanning, but that also provided some measure of functional interaction with the native epitope, thereby

35

resembling the original monoclonal antibody. As shown in Fig. 8, one single clone of 4x bacteriophage clones purified and sequentially tested demonstrated inhibitory activity above background level in a functional platelet assay. This "anti-mimotope" clone displayed the sequence having SEQ ID NO:94: RHVAWWRQGV- the carboxyl terminal half of which is identical to residues 230-234 of GPIb alpha, with only the conservative Lys→Arg substitution at residue 231. (See GPIb alpha sequence from 225-237 [SEQ ID NO:101] and GPIb alpha sequence from 225-234 [SEQ ID NO:173: ENVYVWKQGV]). Of the 97 unique sequences ultimately determined, 9 additional sequences showed varying degrees of structural homology as shown below. Additional anti-mimotope sequences also included the following:

SEQ ID NO:157: AYGVRHLGLS
SEQ ID NO:158: KKWGQHRQRS
20 SEQ ID NO:159: WRWMHWMPHA
SEQ ID NO:160: WHWLAHRHTV
SEQ ID NO:161: RHRHRGFQPR
SEQ ID NO:162: RGWRWHKYWQ
SEQ ID NO:163: KRHAWMKSR
25 SEQ ID NO:164: LLLVGGSELT
SEQ ID NO:165: KKVWMFSYNE
SEQ ID NO:166: LSCRGCRFV
SEQ ID NO:167: HEGCEAQDEL
SEQ ID NO:168: SVRHIWFHVK
30 SEQ ID NO:169: GTWDLWRKGS
SEQ ID NO:170: RWLWPRVHKT
SEQ ID NO:171: HSPFRHVQPR and
SEQ ID NO:172: WVRGHHREVR.

SEQ ID NO:101:

GPIb α 225-237 E N V Y V W K Q G V D V K

SEQ ID NO:94:

R H V A W W R Q G V

SEQ ID NO:95:

A K H R W W R R P V

SEQ ID NO:96:

K H F M R H R H G V

SEQ ID NO:97:

A G L N H W W K H K

SEQ ID NO:98:

R R S T W H W W H A

SEQ ID NO:99:

V A K W R H W N R Q*

Further studies were undertaken with chemically synthesized peptide having SEQ ID NO:94: RHVAWWRQGV. This decapeptide was able to inhibit
5 ristocetin-induced aggregation fully, with an IC_{50} occurring between 200-400 μ g/mL (Fig. 9). A (Gly→Val substitution at position 9 (SEQ ID NO:104), corresponding to the mutation observed in PT-vWD, slightly lowered the IC_{50} , although nearly full
10 inhibition was again seen by 215 μ g/mL. In order to approximate more closely the native structure, peptides with an (Arg→Lys) substitution at position 7 were then studied. As shown in Fig. 10, a more dramatic
15 difference between the Gly and the Val forms of the Lys-containing peptides was observed. Whereas the RHVAWWKQVV (SEQ ID NO:105) peptide retained potent inhibitory activity, the RHVAWWKGVV (SEQ ID NO:106) peptide was unable to exert more than slight
inhibition, except at the highest concentrations tested. Finally, both the wild type GPIb alpha 228-237
20 peptide (SEQ ID NO:108) containing Gly at residue 236 and the PT vWD variant with Val replacing Gly at this position (SEQ ID NO:107) were synthesized. As shown in Fig. 11, the wild-type peptide was virtually without
25 inhibitory activity. In contrast, the peptide corresponding to the PT-vWD mutant was capable of fully inhibiting ristocetin-induced aggregation, with an IC_{50} of approximately 400 μ g/mL. Lyophilized peptides were reconstituted in PBS, pH 6.0 and 150 μ L of varying
30 dilutions incubated for 2-4 hr at 22°C with 250 μ L of formalin-fixed platelets (1.5×10^6 /mL), prior to aggregometry in which the addition of 1 U/mL purified vWF was followed by the addition of 0.9 μ g/mL ristocetin.

35

Three-Dimensional Description of Mimotope/Anti-Mimotope

Figs. 12a-12c show the proposed three dimensional description of mimotopes and anti-mimotopes. In Fig. 12a, the region within the

extracellular domain of platelet glycoprotein Ib alpha containing the original epitope 10 capable of recognizing monoclonal antibody C-34 is shown. Fig. 12b shows the structure of the mimotope peptide 12 which mimics the original epitope (10, as shown in Fig. 12a) in three-dimensional space, without sharing the primary amino acid sequence of the original epitope. The mimotope peptide 12 also recognizes, or binds to, monoclonal antibody C-34.

Fig. 12c illustrates the structure of the mimotope peptide 12 in relation to the structure of the anti-mimotope peptide 14. The anti mimotope peptide sequence is complementary to the face of the mimotope peptide in three-dimensional space, as monoclonal antibody C-34 was to the original epitope (see Fig. 12a).

Epitope Mapping Studies of mab SZ-2

Epitope mapping studies were also conducted using monoclonal antibody SZ-2. The choice of mab SZ-2 (Ruan et al. 1987) was made because its epitope is known to lie within the 45 kDa region of GPIb alpha (Fox et al. 1988; Molino et al. 1993); the epitope is likely to be relatively conformation-independent since SZ-2 binds strongly to GPIb alpha, glyocalicin or GPIb alpha 45kDa fragment that has been denatured in SDS prior to transfer to nitrocellulose (Molino et al. 1993); and there may be widespread interest in epitope localization of this mab since it is available commercially and appears to be being used in a wide variety of investigative and clinical studies worldwide.

The well-balanced, 10-mer random peptide display library was used with SZ-2. Following either two or three rounds of biopanning with immunoscreening in the third round, bacteriophage clones were sequenced and the resulting predicted peptide sequences were analyzed for convergence upon a clear-cut pattern that hopefully is contained within the first ~300 amino

acids of the mature GPIb alpha molecule. The resulting displayed sequences were compared with the available set of glycoprotein sequences known to exist on the platelet surface, including GPIa, GPIb alpha, GPIb β , GPIIb, GPIIIa, GPIV, GPIX, and the platelet FCgamma receptor.

The most convincing correspondence of multiple phage sequences with a natural platelet sequence may be with residues of the platelet FCgamma receptor rather than of GPIb alpha, based upon the following observations. First, while GCG FASTA and WORDSEARCH analyses of phage sequences compared with residues 1-300 of GPIb alpha do show several favored regions of similarity, there is not yet a single, short stretch of amino acids in the native molecule that emerges in a convincing fashion as an obvious match. Second, using the first 50 clones for which highly purified PEG precipitates were prepared and titrated, ELISA assays were performed in which the binding of phage to biotinylated SZ-2 inhibits the subsequent binding of the SZ-2 to immobilized glyccocalicin. Only one of the 50 clones, displaying the sequence having SEQ ID NO:83: W H W R S S W K S G, proved capable of fully neutralizing SZ-2, and no other clone then available came even close in neutralizing potency. This clone, however, did not appear to represent an evident convergent pattern of the series of clones, nor did it provide a more extensive match to sequences within GPIb alpha than other clones then available. In computer-assisted analysis of the other platelet surface proteins, however, this sequence emerged as having the highest FASTA score for the region of the platelet FCgamma receptor shown below, where it is shown as the second peptide in a proposed consensus sequence list. Several additional clones were sequenced, which yielded the peptide shown first in the series - SEQ ID NO:84: H R P L S W K G R A. Note that this peptide also has the SWK sequence, but additionally has an R three residues amino to the SWK.

- 39 -

Below the convergence sequence mapped to the platelet ECgamma receptor is shown in the sequence within GPIb alpha that would most closely match the proposed consensus set.

5

SEQ ID NO:102:

FCGB_HUMAN 148 I V L R C H S W K D K P L V K

SEQ ID NO:84:

H R P L S W K G R A

SEQ ID NO:83:

W H W R S S W K S G

SEQ ID NO:85:

W H R R P M S W Y S

SEQ ID NO:86:

A R I K I W K P R W

SEQ ID NO:87:

K R G W H W K S L H

SEQ ID NO:88:

K K S W W V R M P R

SEQ ID NO:89:

A K S W R Y W R M P

SEQ ID NO:90:

K R W K V Y H R W P

SEQ ID NO:91:

L H R W K Q S P R T

SEQ ID NO:92:

L I R W K P H G W R

SEQ ID NO:93:

Q K K F F S R W K H

SEQ ID NO:103:

GPIb α 221 D N A E N V Y V W K Q G V D V K A M T

SEQ ID NO:91:

L H R W K Q S P R T

SEQ ID NO:83:

W H W R S S W K S G

Although preferred embodiments have been depicted and described in detail herein, it will be apparent to those skilled in the relevant art that various modifications, additions, substitutions and the like can be made without departing from the spirit of the invention and these are therefore considered to be within the scope of the invention as defined in the claims which follow.

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANT: THE RESEARCH FOUNDATION OF
STATE UNIVERSITY OF NEW YORK
- (ii) TITLE OF INVENTION: MIMOTOPES AND ANTI-MIMOTOPES OF
HUMAN PLATELET GLYCOPROTEIN Ib-IX
- (iii) NUMBER OF SEQUENCES: 173
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 - (A) MEDIUM TYPE: Floppy disk
 - (B) COMPUTER: IBM PC compatible
 - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
 - (D) SOFTWARE: PatentIn Release #1.0, Version #1.30
- (vi) CURRENT APPLICATION DATA:
 - (A) APPLICATION NUMBER: PCT of Serial No. 08/556,597,
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 - (C) CLASSIFICATION:
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(2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 10 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Ala Trp Asn Trp Arg Tyr Arg Glu Tyr Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Lys Trp Asn Trp Arg Asn Lys Lys Tyr Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Leu Ser Thr Trp Arg Tyr Phe Glu Tyr Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

- 46 -

Tyr Leu Gly Trp Arg Tyr Ser Glu Tyr Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Thr Gln Met Trp Arg Ala Arg Glu Tyr Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Trp Arg Gln Arg Glu Tyr Trp Asp Pro Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Glu Gly Ser Trp Arg Tyr Arg Lys Gly Gly
1 5 10

(2) INFORMATION FOR SEQ ID NO:8:

- (i) SEQUENCE CHARACTERISTICS:

- 47 -

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Gly Tyr His Trp Trp Arg Asn Trp Glu Tyr
1 5 10

(2) INFORMATION FOR SEQ ID NO:9:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 10 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Lys Gly Phe Leu Trp Arg Ala Arg Asn Trp
1 5 10

(2) INFORMATION FOR SEQ ID NO:10:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 10 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Met Asn Trp Lys His Trp Arg Ala Arg His
1 5 10

(2) INFORMATION FOR SEQ ID NO:11:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 10 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Phe Lys Trp Arg Glu Trp Arg Gly Lys Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Pro Asp Arg Gln Val Arg Leu Trp Val Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Arg Val Leu Arg His Trp His Pro Arg Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Gly Arg Arg Val Trp Met Leu Asn His Gly
1 5 10

(2) INFORMATION FOR SEQ ID NO:15:

- 49 -

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Lys	Lys	Gly	Arg	His	His	Val	Thr	Arg	Val
1				5					10

(2) INFORMATION FOR SEQ ID NO:16:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Gly	Gly	Val	Cys	Lys	Cys	Trp	Gln	Cys	Leu
1				5					10

(2) INFORMATION FOR SEQ ID NO:17:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Phe	Ser	His	Ser	Tyr	Gly	Ser	Ala	Ile	Arg
1				5					10

(2) INFORMATION FOR SEQ ID NO:18:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

- 50 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Met His Gly His Arg Arg Pro Gly Leu Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Met Ser Lys Lys Pro His Leu Gly Leu Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Thr Met Trp Val Glu Leu Tyr Ser Leu Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Phe Val Asp Pro Gly Arg Ala Gly Arg Gly
1 5 10

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Cys Cys Leu Leu Pro Leu Gly Phe Tyr Val Leu Gly Leu Phe Trp Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Phe Arg Cys Cys Val Phe Ser Cys Cys Leu Leu Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Gly Phe Arg Cys Leu Val Ser Leu Gly Gly Cys Phe
1 5 10

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid

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(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Tyr Ser Leu Trp Gly Leu Pro Val Gly Asp Val Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Leu Pro Leu Leu Trp Phe Asn Gly Ala Gly Phe Phe
1 5 10

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Val Trp Gly Leu Phe Arg Gly Leu Glu Asn Gly Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Ser Leu Trp Arg Gln Trp Arg Gly Leu Phe Val Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:29:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Thr Leu Ser Leu Phe Gly Gly Arg Asp Lys Gly Phe
1 5 10

(2) INFORMATION FOR SEQ ID NO:30:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Ile Gly Pro Ala Val Ser Cys Leu Phe Arg Val Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:31:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Met Ser Leu Phe Pro Leu Ser Phe Cys Arg Leu Ile
1 5 10

(2) INFORMATION FOR SEQ ID NO:32:

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- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Ala Leu Phe Ser Ser Val Trp Gly Asp Val Thr Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:33:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Gly Trp Phe Gly Pro Phe Trp Val Arg Gly Ser Gly
1 5 10

(2) INFORMATION FOR SEQ ID NO:34:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Phe Trp Val Ser Val Gly Gly Val Glu Gly Val Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:35:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Leu Gly Ala Phe Gly Gly Ala Gly Phe Leu Trp Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Cys Arg Gly Ile Val Phe Leu Phe Val Gly Trp Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Phe Trp Leu Val Lys Gly Ala Gly Ala Trp Arg Phe
1 5 10

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

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Trp Asn Trp Arg Tyr Arg Glu Tyr Val
 1 5

(2) INFORMATION FOR SEQ ID NO:39:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 12 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Gln Val Arg Leu Trp Ala Arg Ala Gly Ala Gly Gln
 1 5 10

(2) INFORMATION FOR SEQ ID NO:40:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 12 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Gly Leu Ala Val Thr Phe Gly Ser Val Leu Glu Gly
 1 5 10

(2) INFORMATION FOR SEQ ID NO:41:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 12 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Val Arg Trp Met Cys Val Ile Arg Leu Gly Val Arg
 1 5 10

(2) INFORMATION FOR SEQ ID NO:42:

- (i) SEQUENCE CHARACTERISTICS:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Arg Leu Trp Gly Pro Gly Val Ser Arg Pro Val Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Cys Gly Ser Ser Leu Phe Arg Gly Pro Arg Cys Pro
1 5 10

(2) INFORMATION FOR SEQ ID NO:44:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Leu Gly Ile Ser Ser Leu Ser Phe Leu Gln Leu Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:45:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

Thr Trp Gly Trp Asp Gly Val Ser Tyr Leu Phe Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

Thr Arg Ser Leu Phe Asp Asp Phe Val Ser Leu Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

Cys Tyr Ala Ser Leu Phe Arg Ser Arg Leu Cys Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

Asp Gly Ser Val Arg Val Val Trp Val Arg Leu Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:49:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

Leu Ser Gly Phe Pro Val Ala Leu Val Arg Phe Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:50:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Leu Gly Gly Gly Leu Leu Val Gly Ser Val Phe Pro
1 5 10

(2) INFORMATION FOR SEQ ID NO:51:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

Val Trp Ala Arg Gly Val Phe Arg Asp Arg Phe Phe
1 5 10

(2) INFORMATION FOR SEQ ID NO:52:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

Thr	Gly	Leu	Leu	Ala	Gly	Pro	Val	Trp	Arg	Trp	Thr
1				5						10	

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Trp	Leu	Gly	Gly	Ile	Phe	Ser	Cys	Leu	Val	Cys	Gly
1				5						10	

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Trp	Phe	Leu	Arg	Asp	Val	Gly	Cys	Gly	Ser	Cys	Leu
1				5						10	

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

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Ser Arg Cys Gly Val Phe Thr Trp Cys Ser Arg Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:56:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Arg Cys Leu Val Gly Tyr Arg Cys Trp Gly Gly Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:57:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Gly Phe Arg Cys Leu Val Met Gly Gly Gly Cys Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:58:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

Cys Gly Phe Asp Leu Val Cys Ala Arg Leu Phe Gly
1 5 10

(2) INFORMATION FOR SEQ ID NO:59:

- (i) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Asp Ser Gly Val Arg Trp Phe Phe Gly Phe Leu Gly
1 5 10

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Ile Leu Asp Gly Cys Phe Phe Leu Gly Arg Cys Pro
1 5 10

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

Cys Val Arg Trp Leu Val Ser Ala Gly Cys Ser Gly
1 5 10

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Cys	Val	Gly	Cys	Trp	Leu	Val	Cys	Asp	Val	Leu	Leu
1				5					10		

(2) INFORMATION FOR SEQ ID NO:63:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 12 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

Cys	Leu	Phe	Val	Phe	Ala	Ala	Gly	Phe	Ala	Cys	Gly
1				5					10		

(2) INFORMATION FOR SEQ ID NO:64:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 12 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

Ser	Cys	Ala	Leu	Phe	Gly	Ser	Cys	Phe	Gly	Ile	Ser
1				5					10		

(2) INFORMATION FOR SEQ ID NO:65:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 12 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

Cys	Trp	Gly	Gly	Val	Gly	Val	Cys	Gly	Leu	Leu	Val
1				5					10		

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(2) INFORMATION FOR SEQ ID NO:66:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Lys Arg Ala Trp Trp Lys Gln Lys Trp Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:67:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Cys Val Gly Gly Val Ala Ser Arg Cys Gly Val Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:68:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

Ser Gly Ala Val Leu Ala Gly Pro Phe Gly Val Trp
1 5 10

(2) INFORMATION FOR SEQ ID NO:69:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:

12. Use of a polypeptide according to claim 3 for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of at least 8 to about 68 contiguous amino acids selected from the region comprised between amino acid positions 193 to 234 and 243 to 260 in the E1 region of HCV characterized by the following sequence:

QVRNSTGLYHVTNDCPNSSIVYEAHDAILHTPGCVPCVREGN (SEQ ID NO 165, spanning positions 193 to 234), and,
TPTVATTRDGKLPATQLR (SEQ ID NO 105, spanning positions 243 to 260)

with said peptides being particularly chosen from :

QVRNSTGLYHVTNDCPNSSI (SEQ ID NO 16),
NDCPNSSIVYEAHDAILHTP (SEQ ID NO 17),
HDAILHTPGCVPCVREGNVS (SEQ ID NO 18),
CVREGNVSRCWVAMTPTVAT (SEQ ID NO 19), and,
AMTPTVATRDGKLPPATQLRR (SEQ ID NO 20), or any variant to this sequence derived from another type of HCV as depicted in Figure 4, and with said contiguous amino acids containing a T cell stimulating epitope.

13. Use of a polypeptide according to claim 3 for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of at least 8 to about 80 contiguous amino acids selected from the region comprised between amino acids 253 to 332 in the E1 region of HCV characterized by the following sequence:

NH₂-LPATQLRRHIDLLVGSATLCSALYVGDLGSGVQLFTFSPRRH
WTTQGCNCISIYPGHITGHRMAWDMMNWSPTAAL-COOH (SEQ ID NO 106), or any variant to this sequence derived from another type of HCV as depicted in Figure 4, with said peptides being particularly chosen from :

LPATQLRRHIDLLVGSATLC (SEQ ID NO 21),
LVGSATLCSALYVGDLGSGV (SEQ ID NO 22),
QLFTFSPRRHWTTQGCNCISI (SEQ ID NO 23),
TQGCNCISIYPGHITGHRMAW (SEQ ID NO 24), and,
ITGHRMAWDMMNWSPTAAL (SEQ ID NO 25), and with said contiguous

amino acids containing a T cell stimulating epitope.

14. Use of a polypeptide according to claim 3 for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of at least 8 to about 68 contiguous amino acids selected from the region comprised between amino acids 325 to 392 in the E1 region of HCV characterized by the following sequence:

NH₂-MNWSPTAALVMAQLLRIPQAILDMIAGAHWGVLAGIAYFSMVGW

AKVLVLLLLFAGVDAETIVSGGQA-COOH (SEQ ID NO 107), or any variant to this sequence derived from another type of HCV as depicted in Figure 4, with said peptides being particularly chosen from :

NWSPTAALVMAQLLRIPQAI (SEQ ID NO 26),

LLRIPQAILDMIAGAHWGV (SEQ ID NO 27),

AGAHWGVLAGIAYFSMVGW (SEQ ID NO 28), and,

VLLLLFAGVDAETIVSGGQA (SEQ ID NO 29), and with said contiguous amino acids containing a T cell stimulating epitope.

15. Use of a polypeptide according to claim 4 for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to about 20 contiguous amino acids selected from the region comprised between amino acid positions 397 to 416 of the E2 region of HCV:

NH₂-X₃X₃₈X₃₉X₄₀X₄₁X₄₂X₄₃X₄₄X₄₅GX₄₆X₄₇QX₄₈X₄₉X₅₀LX₅₁NX₅₄-COOH (SEQ ID NO 55), and more particularly selected from SGLVSLFTPGAKQNIQLINT (SEQ ID NO 46 or peptide NS1-7'), and with said contiguous amino acids containing a T cell stimulating epitope.

16. Use of a polypeptide according to claim 4 for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to about 20 contiguous amino acids selected from the region comprised between amino acid positions 409 to 428 of the E2 region of HCV:

NH₂-QX₄₈X₄₉X₅₀LX₅₁NX₅₄NGSWHX₅₂NX₅₃TALN-COOH (SEQ ID NO 56),

and more particularly selected from QNIQLINTNGSWHINSTALN (SEQ ID NO 47 or peptide NS1-5'), with said peptides being particularly

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(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

Lys Trp Trp Val Pro Arg His Arg Val Trp
1 5 10

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

Thr Gly Leu Leu Ala Gly Pro Val Trp Arg Trp Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

Asp Ser Gly Val Arg Trp Phe Phe Gly Phe Leu Gly
1 5 10

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Cys Ala Trp His Arg Leu Ser Phe Cys Gly Leu Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

Cys Phe Gly Ser Ala Leu Val Leu Ala Val Leu Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

Trp Phe Trp Asp Met Ser Gly Glu Trp Gly Gly Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

Arg Ser Lys Trp Trp Val His Arg His Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:83:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

Trp His Trp Arg Ser Ser Trp Lys Ser Gly
1 5 10

(2) INFORMATION FOR SEQ ID NO:84:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

His Arg Pro Leu Ser Trp Lys Gly Arg Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:85:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

Trp His Arg Arg Pro Met Ser Trp Tyr Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:86:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:

- 70 -

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

Ala	Arg	Ile	Lys	Ile	Trp	Lys	Pro	Arg	Trp
1			5						10

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

Lys	Arg	Gly	Trp	His	Trp	Lys	Ser	Leu	His
1			5						10

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

Lys	Lys	Ser	Trp	Trp	Val	Arg	Met	Pro	Arg
1			5						10

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

- 71 -

Ala Lys Ser Trp Arg Tyr Trp Arg Met Pro
1 5 10

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

Lys Arg Trp Lys Val Tyr His Arg Trp Pro
1 5 10

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

Leu His Arg Trp Lys Gln Ser Pro Arg Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

Leu Ile Arg Trp Lys Pro His Gly Trp Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:

- 72 -

(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

Gln Lys Lys Phe Phe Ser Arg Trp Lys His
1 5 10

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

Arg His Val Ala Trp Trp Arg Gln Gly Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

Ala Lys His Arg Trp Trp Arg Arg Pro Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

Lys His Phe Met Arg His Arg His Gly Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:97:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

Ala Gly Leu Asn His Trp Trp Lys His Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:98:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

Arg Arg Ser Thr Trp His Trp Trp His Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:99:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

Val Ala Lys Trp Arg His Trp Asn Arg Gln
1 5 10

- 24 -

(2) INFORMATION FOR SEQ ID NO:100:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

CTCATAGTTA GCGTAACG
18

(2) INFORMATION FOR SEQ ID NO:101:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 13 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

Glu Asn Val Tyr Val Trp Lys Gln Gly Val Asp Val Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:102:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

Ile Val Leu Arg Cys His Ser Trp Lys Asp Lys Pro Leu Val Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:103:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 19 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:

- 75 -

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

Asp	Asn	Ala	Glu	Asn	Val	Tyr	Val	Trp	Lys	Gln	Gly	Val	Asp	Val	Lys
1				5				10					15		

Ala Met Thr

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

Arg	His	Val	Ala	Trp	Trp	Arg	Gln	Val	Val
1				5				10	

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

Arg	His	Val	Ala	Trp	Trp	Lys	Gln	Val	Val
1				5				10	

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

Arg His Val Ala Trp Trp Lys Gln Gly Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

Tyr Val Trp Lys Gln Val Val Asp Val Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

Tyr Val Trp Lys Gln Gly Val Asp Val Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

Arg Trp Trp His Trp Val His Arg Glu Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:110:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

Lys Arg Trp Leu Trp Trp Ala Asn Pro Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:111:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

Arg His Leu Trp Trp Gly Gly Arg Met Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:112:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

Arg Leu Trp Pro Gln His Arg Gly His Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:113:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:

- 78 -

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

Lys	Arg	Trp	His	Ile	Arg	Pro	Thr	Ile	Arg
1				5					10

(2) INFORMATION FOR SEQ ID NO:114:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

Lys	Arg	Phe	Lys	Thr	His	Val	His	Gly	Arg
1				5					10

(2) INFORMATION FOR SEQ ID NO:115:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

Thr	Lys	Arg	Phe	Lys	His	Arg	His	Phe	Leu
1				5					10

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

Ala Lys Trp His Trp His Thr Arg Gly Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:117:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

Trp His Arg His Trp Gly Gly Phe Arg Ile
1 5 10

(2) INFORMATION FOR SEQ ID NO:118:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

Trp His Arg Asn Lys Pro Thr Trp His Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:119:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

Trp His Arg Ala Gly Val Arg Ala Lys Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:120:

- (i) SEQUENCE CHARACTERISTICS:

- 80 -

(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

Phe Lys Arg Phe Trp His Thr Gly His Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

Met Met Ala Trp His Ala Arg Val Ala Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

Trp Ile Trp His Arg Pro Ile Lys Val Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

Trp His Arg Thr Leu Pro Lys Arg Gly His
1 5 10

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

Val Lys His Phe Arg Trp Arg Pro Val Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

Lys Arg His Trp Arg Phe Gln Leu Ser Asn
1 5 10

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

Lys Arg His Arg Leu Ala Ser Met Ala Pro
1 5 10

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(2) INFORMATION FOR SEQ ID NO:127:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

Trp Arg Trp Arg Trp Arg Gly Val Leu Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:128:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

Arg Leu His Ala His His Ala Arg His Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:129:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

Arg Trp Gly Ala Lys His Arg Val Arg Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:130:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

Ala	Met	Gly	Trp	Arg	Pro	Val	Lys	His	Arg
1				5					10

(2) INFORMATION FOR SEQ ID NO:131:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

Lys	Trp	Arg	Trp	Arg	Met	His	Gln	His	Tyr
1				5					10

(2) INFORMATION FOR SEQ ID NO:132:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

Trp	Leu	Ser	Lys	Leu	Gly	His	Arg	His	Ala
1				5					10

(2) INFORMATION FOR SEQ ID NO:133:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

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Lys His Cys Ser Ile His Thr Arg Leu Arg
 1 5 10

(2) INFORMATION FOR SEQ ID NO:134:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 10 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

Gly Ser Ala Glu Arg Met Ser Glu Gly His
 1 5 10

(2) INFORMATION FOR SEQ ID NO:135:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 10 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

Phe Pro Leu Trp Asn Val Leu Thr Met Thr
 1 5 10

(2) INFORMATION FOR SEQ ID NO:136:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 12 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:

Ser Phe Ala Gly Val Gly Trp Phe Ala Leu Gly
 1 5 10

(2) INFORMATION FOR SEQ ID NO:137:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

Cys Asp Leu Trp Val Cys Phe Leu Asp Gly Gly Gly
1 5 10

(2) INFORMATION FOR SEQ ID NO:138:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:138:

Leu Val Ala Arg Phe Pro Pro Pro Tyr Gly Gly Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:139:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

Ser Ile Val Trp Leu Thr Arg Pro Lys Gly
1 5 10

(2) INFORMATION FOR SEQ ID NO:140:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

Cys Arg Tyr Arg Ala Leu Asn Gly Val Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:141:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:141:

Ala Leu Thr Ser Arg Thr Trp Ala Arg Gln
1 5 10

(2) INFORMATION FOR SEQ ID NO:142:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:

Thr Arg Tyr Met Leu Ser Arg Gln Ser Asn
1 5 10

(2) INFORMATION FOR SEQ ID NO:143:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:143:

(2) INFORMATION FOR SEQ ID NO:144:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(11) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:144:

Trp Arg Arg His Val Pro Leu Arg Ile Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:145:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 10 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:145:

phe His Arg Trp Asn Arg Pro Met Val Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:146:

(1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 10 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:146:

His Arg Tyr Lys Lys Thr Pro Val Pro Met
1 5 10

(2) INFORMATION FOR SEQ ID NO:147:

(i) SEQUENCE CHARACTERISTICS:

- 88

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:147:

Trp Leu His Val Lys Arg Arg Pro Val Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:148:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 10 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:148:

Trp Val Arg His Lys His Pro Ile Val Pro
1 5 10

(2) INFORMATION FOR SEQ ID NO:149:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 10 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:149:

Leu Ser Met Arg Arg Arg Gln Phe Gln Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:150:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 10 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:150:

Phe His Trp Arg Asp Lys Trp Arg Thr Gly
1 5 10

(2) INFORMATION FOR SEQ ID NO:151:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:151:

Arg Met Arg Arg Pro Gly Ile Thr Val Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:152:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:152:

Gly His Arg Trp Asn Arg Pro Met Val Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:153:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:153:

Trp His Arg His Thr Pro Lys Arg Ile Pro
1 5 10

(2) INFORMATION FOR SEQ ID NO:154:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:154:

Trp His Trp Gln Arg Ser Arg Pro Ala Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:155:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:155:

Lys Arg Thr Trp Trp His Tyr Ile Arg Pro
1 5 10

(2) INFORMATION FOR SEQ ID NO:156:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:156:

Lys Arg Trp Arg His Ser Leu Pro Ala Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:157:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:157:

Ala	Tyr	Gly	Val	Arg	His	Leu	Gly	Leu	Ser
1				5					10

(2) INFORMATION FOR SEQ ID NO:158:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:158:

Lys	Lys	Trp	Gly	Gln	His	Arg	Gln	Arg	Ser
1				5					10

(2) INFORMATION FOR SEQ ID NO:159:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:159:

Trp	Arg	Trp	Met	His	Trp	Met	Pro	His	Ala
1				5					10

(2) INFORMATION FOR SEQ ID NO:160:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:160:

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Trp His Trp Leu Ala Arg His Arg Thr Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:161:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:161:

Arg His Arg His Arg Gly Phe Gln Pro Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:162:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:162:

Arg Gly Trp Arg Trp His Lys Tyr Trp Gln
1 5 10

(2) INFORMATION FOR SEQ ID NO:163:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:163:

Lys Arg His Ala Trp Met Lys Ser Arg Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:164:

- (i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:164:

Leu	Leu	Leu	Val	Gly	Gly	Ser	Glu	Leu	Thr
1				5					10

(2) INFORMATION FOR SEQ ID NO:165:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 10 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:165:

Lys	Lys	Val	Trp	Met	Phe	Ser	Tyr	Asn	Glu
1				5					10

(2) INFORMATION FOR SEQ ID NO:166:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 10 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:166:

Leu	Ser	Cys	Arg	Gly	Cys	Arg	Ala	Phe	Val
1				5					10

(2) INFORMATION FOR SEQ ID NO:167:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 10 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:167:

His Glu Gly Cys Glu Ala Gln Asp Glu Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:168:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:168:

Ser Val Arg His Ile Trp Phe His Val Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:169:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:169:

Gly Thr Trp Asp Leu Trp Arg Lys Gly Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:170:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:170:

Arg Trp Leu Trp Pro Arg Val His Lys Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:171:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 10 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:171:

His	Ser	Pro	Phe	Arg	His	Val	Gln	Pro	Arg
1				5					10

(2) INFORMATION FOR SEQ ID NO:172:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 10 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:172:

Trp	Val	Arg	Gly	His	His	Arg	Glu	Val	Arg
1				5					10

(2) INFORMATION FOR SEQ ID NO:173:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 10 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:173:

Glu	Asn	Val	Tyr	Val	Trp	Lys	Gln	Gly	Val
1				5					10

WHAT IS CLAIMED IS:

1. An isolated peptide that functionally mimics a binding site for a monoclonal antibody, the monoclonal antibody recognizing an epitope within the human platelet glycoprotein Ib-IX complex.

2. The isolated peptide of claim 1 wherein the monoclonal antibody is designated C 34.

3. The isolated peptide of claim 1 wherein said peptide includes an amino acid sequence selected from the group consisting of:

15	SEQ ID NO:1:	AWNWRYREYV
	SEQ ID NO:2:	KWNWRNKKYV
	SEQ ID NO:3:	LSTWRYFEYV
	SEQ ID NO:4:	YLGWRYSEYV
	SEQ ID NO:	TQMWRAREYL
20	SEQ ID N	WRQREYWDPV
	SEQ ID N	ESSWIRKGG
	SEQ ID N	GYHWLRNWEY
	SEQ ID NO:9:	KGFLWRARNW
	SEQ ID NO:10:	MNWKHWRARH
25	SEQ ID NO:11:	FKWREWRGKL
	SEQ ID NO:12:	PDRQVRLWVR
	SEQ ID NO:13:	RVLRRHWHPR
	SEQ ID NO:14:	GRRVWMLNHG
	SEQ ID NO:15:	KKGRHHVTRV
30	SEQ ID NO:16:	GGVCKCWQCL
	SEQ ID NO:17:	FSHSYCSAIR
	SEQ ID NO:18:	MHGHRFPGLA
	SEQ ID NO:19:	MSKKPHLGLR
	SEQ ID NO:20:	TMWVELYSLK
35	SEQ ID NO:21:	FVDPGRAGRG
	SEQ ID NO:23:	FRCCVFSCCLLS
	SEQ ID NO:24:	GFRCLVSLGGCF
	SEQ ID NO:25:	YSLWGLPVGDVV
	SEQ ID NO:26:	LPLLWFNGAGFF

SEQ ID NO:27: VWGLFRGLENGS
SEQ ID NO:28: SLWRQWRGLFVV
SEQ ID NO:29: TLSLFGGRDKGF
SEQ ID NO:30: IGPAVSCLEFRVC
5 SEQ ID NO:31: MSLFPLSFCRLI
SEQ ID NO:32: ALFSSVWGDVTL
SEQ ID NO:33: GWFGPFWVRGSG
SEQ ID NO:34: FWVSVGGVEGVV
SEQ ID NO:35: LGAFGGAGFLWR
10 SEQ ID NO:36: CRGIVFLFVQWL
SEQ ID NO:37: FWLVKGAGAWRF
SEQ ID NO:39: QVRLWARAGAQQ
SEQ ID NO:40: GLAVTFGSLVLE
SEQ ID NO:41: VRWMCVIRLGVR
15 SEQ ID NO:42: RLWGPVSRPVL
SEQ ID NO:43: CGSSLFRGPRCP
SEQ ID NO:44: LGISLFLQLF
SEQ ID NO:45: TWGWDGVSYLFL
SEQ ID NO:46: TRSLFDDFVSLR
20 SEQ ID NO:47: CYASLFRSRLCA
SEQ ID NO:48: DGSVRVWVRL
SEQ ID NO:49: LSGFPVALVREA
SEQ ID NO:50: LSGGLLVGSVEF
SEQ ID NO:51: VWARGVFRDRFF
25 SEQ ID NO:52: TGLLAGPVWRWT
SEQ ID NO:53: WLGGIFSCLVCG
SEQ ID NO:54: WFLRDVGGGCL
SEQ ID NO:55: SRCGVFTWCSRS
SEQ ID NO:56: RCLVGYRCWGGV
30 SEQ ID NO:57: GFRCLVMGGGCA
SEQ ID NO:58: CGFDLVCARLFG
SEQ ID NO:59: DSGVRWFFGFLG
SEQ ID NO:60: ILDGCFFLGRCP
SEQ ID NO:61: CVRWLVSAAGCSG
35 SEQ ID NO:62: CVGCWLVCVLL
SEQ ID NO:63: CLFVFAAGFACG
SEQ ID NO:64: SCALFGSCFGIS
SEQ ID NO:65: CWGGVGVCGLLV
SEQ ID NO:66: KRAWWKQKWV

SEQ ID NO:67: CVGGVASRCGVL
 SEQ ID NO:68: SGAVLAGPFGVW
 SEQ ID NO:69: CRAFDRVGVGVW
 SEQ ID NO:70: RCLVGYVVGGVW
 5 SEQ ID NO:71: VCLVYRSVDCWA
 SEQ ID NO:72: WRVVFVFTCVVWA
 SEQ ID NO:73: LWREWRGLFAVL
 SEQ ID NO:74: SGAVLAGPLWRL
 SEQ ID NO:75: FVVRGGTFLFVR
 10 SEQ ID NO:76: TGLLAGPVWRWT
 SEQ ID NO:78: DSGVRWFFGFLG
 SEQ ID NO:79: CAWHRLSFCGLV
 SEQ ID NO:80: CFSSALVLAVIA and
 SEQ ID NO:81: WFWDMSSGEWGGL

15

4. The isolated peptide of claim 2 wherein said peptide includes an amino acid sequence corresponding to SEQ ID NO: 38: WNWRYREYV.

20

5. A fragment of the isolated peptide of claim 3, wherein the fragment functionally mimics the binding site for monoclonal antibody C-34.

25

6. The fragment of claim 4 wherein said fragment has an amino acid sequence corresponding to SEQ ID NO:38: WNWRYREYV.

30

7. The isolated peptide of claim 1 wherein the monoclonal antibody is designated SZ-2.

35

8. The isolated peptide of claim 7 wherein said peptide includes an amino acid sequence selected from the group consisting of:

SEQ ID NO:83: WHWESSWKSG
 SEQ ID NO:84: HRFLSWKGRA
 SEQ ID NO:85: WHRRPMSWYS
 SEQ ID NO:86: ARIKIWKPRW
 SEQ ID NO:87: LRGWHWKSLLH

SEQ ID NO:88: EKSWWVRMPR
SEQ ID NO:89: AKSWRYWRMP
SEQ ID NO:90: ERWKVYHRWP
SEQ ID NO:91: LHRWKQSPRT
5 SEQ ID NO:92: LIRWKPHGWR
SEQ ID NO:93: QKKFFSRWKH
SEQ ID NO:94: KWWVPRHRVW
SEQ ID NO:95: RSKWWVHRHS
SEQ ID NO:96: RWWHWVHRET
10 SEQ ID NO:110: ERWLWWANPR
SEQ ID NO:111: EHLWWGGRMK
SEQ ID NO:112: ELWPQHRGHR
SEQ ID NO:113: ERWHIRPTIR
SEQ ID NO:114: HRFKTHVHGR
15 SEQ ID NO:115: TKRFKHRHFL
SEQ ID NO:116: AKWHWHTRGR
SEQ ID NO:117: WHRHWWGGFRI
SEQ ID NO:118: WHRNKPTWHS
SEQ ID NO:119: WHRAGVRAKV
20 SEQ ID NO:120: FKRFWHTGHE
SEQ ID NO:121: MMAWHARVAR
SEQ ID NO:122: WIWHRPIKVK
SEQ ID NO:123: WHRTLPRKRGH
SEQ ID NO:124: VKHFRWEPVA
25 SEQ ID NO:125: KRHWRFQLSN
SEQ ID NO:126: KRHRLASMAP
SEQ ID NO:127: WRWRWRGVLR
SEQ ID NO:128: PLHAHHARHE
SEQ ID NO:129: RWGAKHRVRV
30 SEQ ID NO:130: AMGWRPVKHE
SEQ ID NO:131: KWRWRMHQHY
SEQ ID NO:132: WLSKLGRHRA
SEQ ID NO:133: KHCSIHTRLR
SEQ ID NO:134: GSAERMSEGH
35 SEQ ID NO:135: EPLWNVLTMT
SEQ ID NO:136: SFAGVGWFALLG
SEQ ID NO:137: CDLWVCFDGGG
SEQ ID NO:138: LVARFPPPYGGV
SEQ ID NO:139: SIVWLTRPKG

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SEQ ID NO:140: CRYRALNSVL
SEQ ID NO:141: ALTSRTWARQ
SEQ ID NO:142: TRYMLSRQSN
SEQ ID NO:143: AMREARITVK
5 SEQ ID NO:144: WRRHVPLRIL
SEQ ID NO:145: FHRWNRPMVT
SEQ ID NO:146: HRYKKTPVPM
SEQ ID NO:147: WLHVHRRPVV
SEQ ID NO:148: WVRHKHFIVP
10 SEQ ID NO:149: LSMRRRQFQS
SEQ ID NO:150: FHWREKWRTO
SEQ ID NO:151: RMRRPGITVK
SEQ ID NO:152: GHRWNEPMVT
SEQ ID NO:153: WRRHTFKRIP
15 SEQ ID NO:154: WHWQSRPAL
SEQ ID NO:155: KRTWWHYIRP and
SEQ ID NO:156: KRWRHSLPAS.

9. An isolated molecule capable of binding
20 to the peptide of claim 1.

10. The isolated molecule of claim 9 wherein
said molecule is chemically synthesized.

25 11. The isolated molecule of claim 9 wherein
the molecule comprises an antibody.

12. The isolated molecule of claim 9 wherein
the molecule comprises a second peptide.

30 13. The isolated molecule of claim 12
wherein said second peptide includes an amino acid
sequence selected from the group consisting of:

35 SEQ ID NO:94: RHVAWWRQGV
SEQ ID NO:95: AKHRWWREPV
SEQ ID NO:96: KHFMRRRHGV
SEQ ID NO:97: AGLNHWWKHK
SEQ ID NO:98: RRSTWHWWHA

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SEQ ID NO:99: VAKWRHWNRRQ
SEQ ID NO:157: AYGVRHLGLS
SEQ ID NO:158: KKWGQHRQRS
SEQ ID NO:159: WRWMHWMFHA
5 SEQ ID NO:160: WHWLARHETV
SEQ ID NO:161: RHRHRGFQPR
SEQ ID NO:162: RGWRWHKYWQ
SEQ ID NO:163: KRHAWMKSRL
SEQ ID NO:164: LLLVGGSELT
10 SEQ ID NO:165: KKVWMFSYNE
SEQ ID NO:166: LSCRGCFRAFV
SEQ ID NO:167: HEGCEAQDEL
SEQ ID NO:168: SVRHIWFHVK
SEQ ID NO:169: GTWDLWRKGS
15 SEQ ID NO:170: RWLWPRVHKT
SEQ ID NO:171: HSPFRHVQPR and
SEQ ID NO:172: WVRGHHREVR.

14. The isolated molecule of claim 9 wherein
20 the molecule is selected from the group consisting of a
DNA molecule and an RNA molecule.

15. A method of modulating the adhesion,
aggregation, or agglutination of platelets, which
25 method comprises selecting platelets and exposing said
platelets to the molecule of claim 3, thereby affecting
von Willebrand factor interaction with platelets
through the glycoprotein Ib/IX receptor and modulating
the adhesion, aggregation, or agglutination of said
30 platelets.

16. An isolated peptide capable of binding
to monoclonal antibody C-34, the peptide including an
amino acid sequence selected from the group consisting
35 of:

SEQ ID NO:1: AWNWRYREYV
SEQ ID NO:2: KWNWRNKKYV
SEQ ID NO:3: LSTWRYFEYV

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SEQ ID NO:4: YLSWRYSEYV
SEQ ID NO:5: TQMWRAREYL
SEQ ID NO:6: WRQREYWDPV
SEQ ID NO:7: EGSWRYRKGG
5 SEQ ID NO:8: GYHWWRIWEY
SEQ ID NO:9: KGFLWRARNW
SEQ ID NO:10: MNWKHWRARH
SEQ ID NO:11: FKWREWRGKL
SEQ ID NO:12: PDRQVRLWVR
10 SEQ ID NO:13: RVLKHHWHPT
SEQ ID NO:14: GRRVWMLNHG
SEQ ID NO:15: KKGRHHVTRY
SEQ ID NO:16: GGVCKCWQCL
SEQ ID NO:17: FSHSYGSAIK
15 SEQ ID NO:18: MHGHRREFGLA
SEQ ID NO:19: MSKKFHLGLR
SEQ ID NO:20: TMWVELYSLK
SEQ ID NO:21: FVDPGRAGRG
SEQ ID NO:23: FRCCVFSCOLLS
20 SEQ ID NO:24: GFRCLVSLGGCF
SEQ ID NO:25: YSLW3LPVGDVV
SEQ ID NO:26: LPLLWFNGA3FF
SEQ ID NO:27: VWGLFRGLENGS
SEQ ID NO:28: SLWRQWR3LEVV
25 SEQ ID NO:29: TLSLEGGGRDKGF
SEQ ID NO:30: IGPVVSCLFRVC
SEQ ID NO:31: MSLFPPLSFCRLI
SEQ ID NO:32: ALFSS3VWGDVTL
SEQ ID NO:33: GWFGPFWVRGSG
30 SEQ ID NO:34: FWVSVGGVEGVV
SEQ ID NO:35: LGAFGGAGFLWR
SEQ ID NO:36: CRGIVFLFVGWL
SEQ ID NO:37: FWLVKGAGAWRF
SEQ ID NO:39: QVRLWARAGAGQ
35 SEQ ID NO:40: GLAVTFGSVLEG
SEQ ID NO:41: VRWMCVIRLGVR
SEQ ID NO:42: RLWGPQVSRPVL
SEQ ID NO:43: CGSSSLFRGPRCP
SEQ ID NO:44: LGISSLSFLQLR

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SEQ ID NO:45: TWGWDGVSYLFL
SEQ ID NO:46: TRSLFDDFVSLR
SEQ ID NO:47: CYASLFRSRLCA
SEQ ID NO:48: DGSVRVWVRLL
5 SEQ ID NO:49: LSGFPVALVRFA
SEQ ID NO:50: LGGGLLVGSVFP
SEQ ID NO:51: VWARGVFRDRFF
SEQ ID NO:52: TGLLAGPVWRWT
SEQ ID NO:53: WLGGIFSCLVCG
10 SEQ ID NO:54: WFLRDVCGCSCL
SEQ ID NO:55: SRCGVFTWCSRS
SEQ ID NO:56: RCLVGYRCWGGV
SEQ ID NO:57: GFRCLVMGGGCA
SEQ ID NO:58: CGFDLVCARLFG
15 SEQ ID NO:59: DSGVRWFFGFLG
SEQ ID NO:60: ILDGCFFLGRCP
SEQ ID NO:61: CVRWLVSAAGCSG
SEQ ID NO:62: CVGCWLVCDEVLL
SEQ ID NO:63: CLFVFAAGFACG
20 SEQ ID NO:64: SCALFGSCFGIS
SEQ ID NO:65: CWGGVGVCGLLV
SEQ ID NO:66: KRAWWKQKWV
SEQ ID NO:67: CVGGVASRCGVL
SEQ ID NO:68: SGAVLAGPFGVW
25 SEQ ID NO:69: CRAFDRVGVVCVW
SEQ ID NO:70: RCLVGYVVGGVW
SEQ ID NO:71: VCLVYRSVDCWA
SEQ ID NO:72: WRVVFVTCVVWA
SEQ ID NO:73: LWREWRGLFAVL
30 SEQ ID NO:74: SGAVLAGPLWRL
SEQ ID NO:75: FVVRGGTFLFVR
SEQ ID NO:77: TGLLAGPVWRWT
SEQ ID NO:78: DSGVRWFFGFLG
SEQ ID NO:79: CAWHRLSFCGLV
35 SEQ ID NO:80: CFGSALVLAVLA and
SEQ ID NO:81: WFDMSGGEWGGL.

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17. A fragment of the isolated peptide of claim 16, wherein the fragment is capable of binding to monoclonal antibody C-34.

18. The fragment of claim 17, wherein said fragment has an amino acid sequence corresponding to SEQ ID NO:38: WNWRVREYV.

19. An isolated molecule capable of binding to the peptide of claim 16.

20. The isolated molecule of claim 19, wherein said molecule is chemically synthesized.

21. The isolated molecule of claim 19, wherein the molecule comprises an antibody.

22. The isolated molecule of claim 19, wherein the molecule comprises a second peptide.

23. The isolated molecule of claim 22 wherein said second peptide includes an amino acid sequence selected from the group consisting of:

25 SEQ ID NO:94: RHVAWWRQGV
SEQ ID NO:95: AKHRWWRPVP
SEQ ID NO:96: KHFMRRRHGV
SEQ ID NO:97: AGLNHWWFKHK
SEQ ID NO:98: RRSTWHWWHA
30 SEQ ID NO:99: VAKWRHWNRC
SEQ ID NO:157: AYGVRHLGLS
SEQ ID NO:158: KKWGQHRQRS
SEQ ID NO:159: WRWMHWMFHA
SEQ ID NO:160: WHWLARHRTV
35 SEQ ID NO:161: RHRHRGFQPR
SEQ ID NO:162: RGWRWHKYWQ
SEQ ID NO:163: KRHAWMKSRL
SEQ ID NO:164: LLLVGGSELT
SEQ ID NO:165: KKVWMFSYNE

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SEQ ID NO:166: LSCRGCRAPV
SEQ ID NO:167: HEGCEAQDEL
SEQ ID NO:168: SVRHIWFHVK
SEQ ID NO:169: GTWDLWRKGS
5 SEQ ID NO:170: RWLWPRVHKT
SEQ ID NO:171: HSPFRHVQPR and
SEQ ID NO:172: WVRGHHREVR.

24. The isolated molecule of claim 19,
10 wherein the molecule is selected from the group
consisting of a DNA molecule and an RNA molecule.

25. A method of modulating the adhesion,
aggregation, or agglutination of platelets, which
15 method comprises selecting platelets and exposing said
platelets to the molecule of claim 19, thereby
affecting von Willebrand factor interaction with
platelets through the glycoprotein Ib/IX receptor and
modulating the adhesion, aggregation, or agglutination
20 of said platelets.

26. An isolated peptide capable of binding
to monoclonal antibody C-34, the peptide including an
amino acid sequence corresponding to SEQ ID NO:38:
25 WNWRYREYV.

27. An isolated peptide capable of binding
to monoclonal antibody SZ-2, the peptide including an
amino acid sequence selected from the group consisting
30 of:

SEQ ID NO:83: WHWRSSWKSG
SEQ ID NO:84: HRPLSWKGRA
SEQ ID NO:85: WHRRPMSWYS
35 SEQ ID NO:86: ARIKIWKPRW
SEQ ID NO:87: KRGWHWKSLE
SEQ ID NO:88: KKSWWVRMPR
SEQ ID NO:89: AKSWRYWRMP
SEQ ID NO:90: ERWKVYHEWF

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SEQ ID NO:91: LHRWKQSPRT
SEQ ID NO:92: LIRWKPHGWR
SEQ ID NO:93: QKKFFSRWKH
SEQ ID NO:76: KWWVPRHRVW
5 SEQ ID NO:82: RSKWWVHRHS
SEQ ID NO:109: RWWHWVHRET
SEQ ID NO:110: KRWLWWANFR
SEQ ID NO:111: RHLWWGGRMK
SEQ ID NO:112: RLWPQHRGHR
10 SEQ ID NO:113: RRVHIRTIR
SEQ ID NO:114: RRFKTHVHGR
SEQ ID NO:115: TRRFKRRHFL
SEQ ID NO:116: AKWHWHTRGR
SEQ ID NO:117: WHRHWWGGFRI
15 SEQ ID NO:118: WHRNKPTWHS
SEQ ID NO:119: WHRAGVRAKV
SEQ ID NO:120: FKRFWHTGHR
SEQ ID NO:121: MMAWHARVAR
SEQ ID NO:122: WIWHRPIKVK
20 SEQ ID NO:123: WHRTLPRGRH
SEQ ID NO:124: VKHFRWRPVA
SEQ ID NO:125: KRWRFQLSN
SEQ ID NO:126: KRHRLASMAP
SEQ ID NO:127: WRWRWRGVLE
25 SEQ ID NO:128: RLHAHHARHE
SEQ ID NO:129: RWGAKHRVRV
SEQ ID NO:130: AMGWRPVKHR
SEQ ID NO:131: KWRWRMHQHY
SEQ ID NO:132: WLSKLGRHA
30 SEQ ID NO:133: KHCSIHTRLR
SEQ ID NO:134: GSAERMSEGH
SEQ ID NO:135: FPLWNVLTMT
SEQ ID NO:136: SFAGVGWFALLG
SEQ ID NO:137: CDLWVCFLDGGG
35 SEQ ID NO:138: LVARFPPPYGGV
SEQ ID NO:139: SIVWLTRPKG
SEQ ID NO:140: CRYRALNGVL
SEQ ID NO:141: ALTSRTWARQ
SEQ ID NO:142: TRYMLSRQSN

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SEQ ID NO:143: AMREARITVK
SEQ ID NO:144: WRRHVPLRIL
SEQ ID NO:145: FHRWNRPMVT
SEQ ID NO:146: HRYKKTPVPM
5 SEQ ID NO:147: WLHVKKRPVV
SEQ ID NO:148: WVRHKKHPIVP
SEQ ID NO:149: LSMRRRQFQS
SEQ ID NO:150: FHWRDKWRTG
SEQ ID NO:151: RMRRPGITVK
10 SEQ ID NO:152: GHRWNRPMVT
SEQ ID NO:153: WHRHTFKRIP
SEQ ID NO:154: WHWQRSPAL
SEQ ID NO:155: KRTWWHYIRP and
SEQ ID NO:156: KRWRHSLPAS..

15

28. A fragment of the isolated peptide of claim 27, wherein the fragment is capable of binding to monoclonal antibody SZ-2.

20

29. An isolated molecule capable of binding to the peptide of claim 27.

25

30. The isolated molecule of claim 29, wherein said molecule is chemically synthesized.

31. The isolated molecule of claim 29, wherein the molecule comprises an antibody.

30

32. The isolated molecule of claim 29, wherein the molecule comprises a second peptide.

35

33. The isolated molecule of claim 29, wherein the molecule is selected from the group consisting of a DNA molecule and an RNA molecule.

34. A method of modulating the adhesion, aggregation, or agglutination of platelets, which method comprises selecting platelets and exposing said platelets to the molecule of claim 29, thereby

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affecting von Willebrand factor interaction with platelets through the glycoprotein Ib/IX receptor and modulating the adhesion, aggregation, or agglutination of said platelets.

5

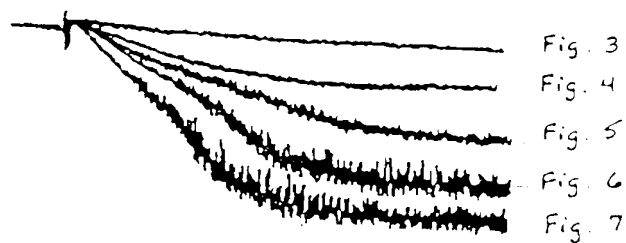
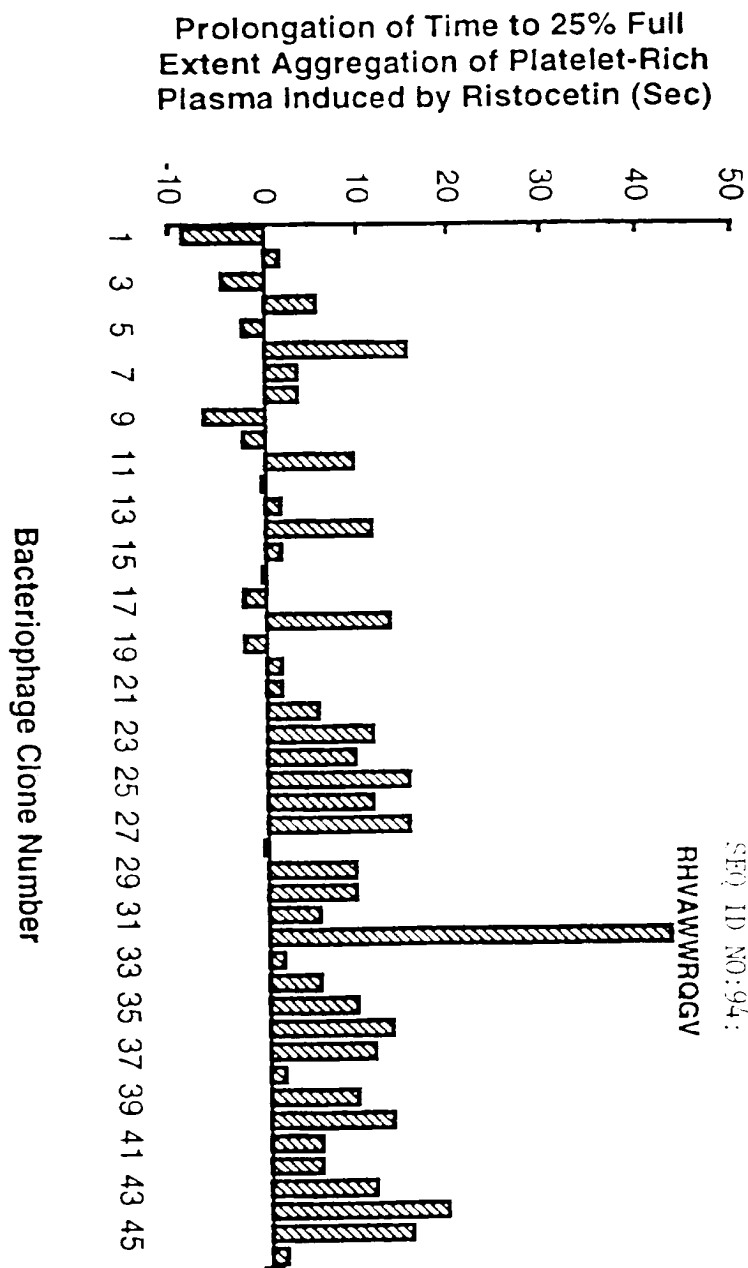


FIG. 8



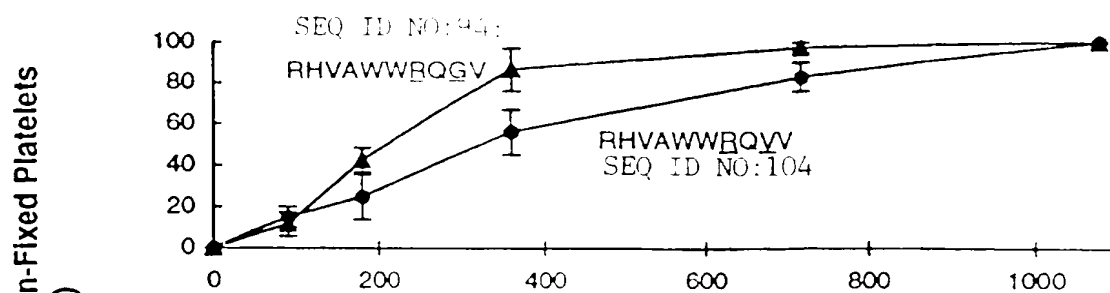


FIG. 9

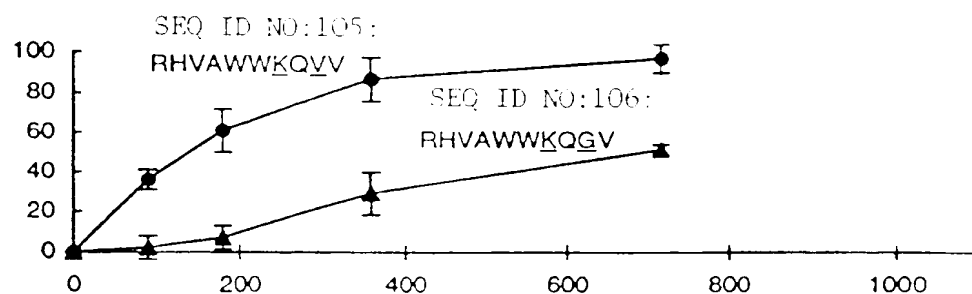


FIG. 10

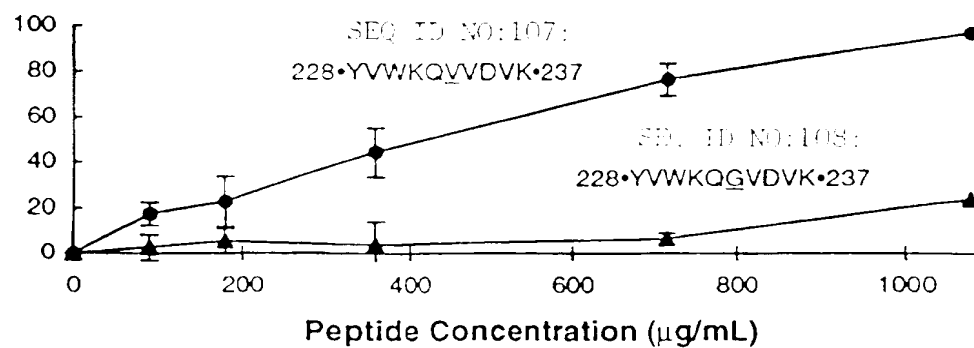


FIG. 11

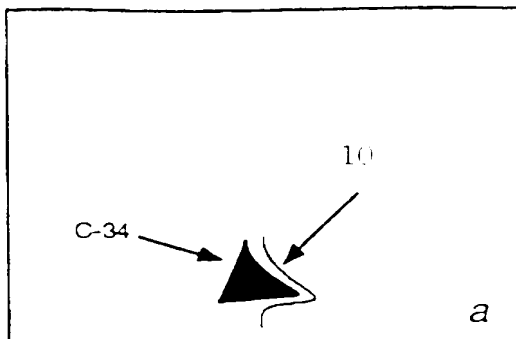


Fig. 12a

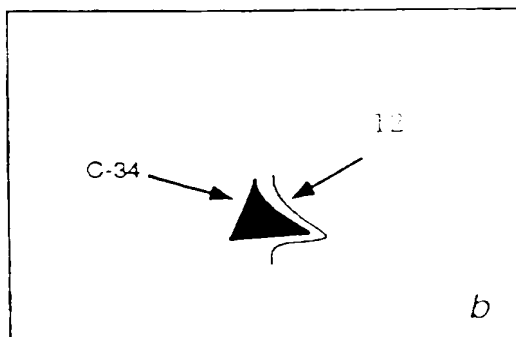


Fig. 12b

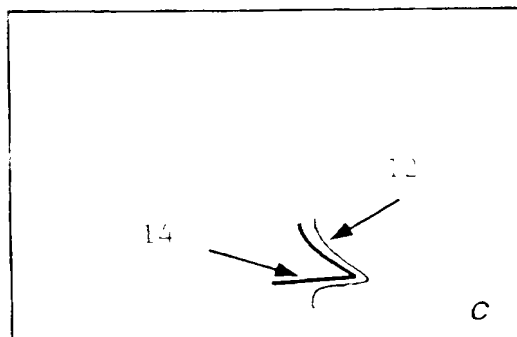


Fig. 12c

INTERNATIONAL SEARCH REPORT

International application No
PCT/US96/17882**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : C07K 7/06; A61K 38/08

US CL : 530/300, 328, 380; 424/185.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U S : 530/300, 328, 380; 424/185.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Automated patent system (APS), DIALOG key words: platelet glycoprotein Ib/IX complex, peptide, C-34, SZ-2

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SOUTH et al., Identification of novel peptide antagonists for von Willebrand Factor binding to the Platelet Glycoprotein Ib Receptor from a phage epitope library. Thrombosis and Haemostasis. 1995, Vol. 73, No. 1, pages 144-150, see abstract.	1-34
Y	MILLER et al. Increased platelet sensitivity to ristocetin is predicted by the binding characteristics of a GPIb/IX determinant. British J. Haematology. 1990, Vol. 74, pages 313-319, see Summary on page 313.	1-34
Y	SCOTT et al. Searching for peptide ligands with an epitope library. Science. 27 July 1990, Vol. 249, pages 386-390, see entire document.	1-34

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

*	Special categories of cited documents	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search

13 FEBRUARY 1997

Date of mailing of the international search report

19 MAR 1997

Name and mailing address of the ISA/US
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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No
PCT/US96/17882

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos. because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos. because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos. because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1

Group I, claims 1, 7-8, and 27-28, drawn to peptides that mimic a binding site for monoclonal antibody SZ-2, that binds to an epitope of glycoprotein Ib/IX complex

Group II, claims 1-6, 16-18, and 26, drawn to peptide mimetopes that mimic a binding site for monoclonal antibody C34 which recognizes an epitope of glycoprotein Ib/IX.

Group III, claims 9-15, 19-25 and 29-34, drawn to anti-mimetic molecules capable of binding to the molecules that bind to monoclonal antibodies binding glycoprotein Ib/IX complex and to methods of modulating adhesion using such molecules.

The inventions listed as Groups I-III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: each group of peptides binds to a distinct substrate, either monoclonal antibody C34, SZ-2 or to peptides which bind to monoclonal antibody C34. Each claimed peptide has a materially different amino acid sequence and requires a separate search.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. Office practice requires the examination of the first ten SEQ ID NO's as a single invention. Each four additional SEQ ID NO's represents an additional invention for which an additional fee must be paid. The species are as follows:

For Group I:

Species 1-16 = the peptides of SEQ ID NOS. 83-86, 87-90, 91-93 and 76, 82 and 109-111, 112-115, 116-119, 120-123, 124-127, 128-131, 132-135, 136-139, 140-143, 144-147, 148-151, 152-155, 156.

For Group II:

Species 1-18 = the peptides of SEQ ID NOS. 1-10, 11-14, 15-18, 19-21 and 23, 24-27, 28-31, 32-35, 36-37 and 39-40, 41-44, 45-48, 49-52, 53-56, 57-60, 61-64, 65-68, 69-72, 73-75 and 77, 78-81.

For Group III:

Species 1 = the claims of Group I as they encompass the peptides recited by claim 13.

Species 2 = isolated molecules as encompassing antibodies, e.g. claim 11, 21 and 31

Species 3 = isolated molecules as encompassing DNA or RNA, e.g. claims 14, 24 and 33

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each group of peptides or products has a materially different structure, e.g. a different chemical structure, such as DNA, RNA or protein or a different protein structure as indicated by diverse amino acid sequences.

